ISSN 2218-4333 (online)

World Journal of *Clinical Oncology*

World J Clin Oncol 2024 June 24; 15(6): 667-785

Published by Baishideng Publishing Group Inc

World Journal of Clinical Oncology

Contents

Monthly Volume 15 Number 6 June 24, 2024

EDITORIAL

REVIEW

ORIGINAL ARTICLE

Retrospective Study

World Journal of Clinical Oncology

Monthly Volume 15 Number 6 June 24, 2024

Contents

World Journal of Clinical Oncology

Monthly Volume 15 Number 6 June 24, 2024

Contents

ABOUT COVER

Editorial Board Member of *World Journal of Clinical Oncology*, Qiang Huo, MD, MSc(Med), Doctor-in-charge, Center for Translational Medicine, Zibo Central Hospital, No. 54 West Gongqingtuan Road, Zibo 255036, Shandong Province, China. qianghuo@mail.sdu.edu.cn

AIMS AND SCOPE

The primary aim of *World Journal of Clinical Oncology* (*WJCO*, *World J Clin Oncol*) is to provide scholars and readers from various fields of oncology with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

WJCO mainly publishes articles reporting research results and findings obtained in the field of oncology and covering a wide range of topics including art of oncology, biology of neoplasia, breast cancer, cancer prevention and control, cancer-related complications, diagnosis in oncology, gastrointestinal cancer, genetic testing for cancer, gynecologic cancer, head and neck cancer, hematologic malignancy, lung cancer, melanoma, molecular oncology, neurooncology, palliative and supportive care, pediatric oncology, surgical oncology, translational oncology, and urologic oncology.

INDEXING/ABSTRACTING

The *WJCO* is now abstracted and indexed in PubMed, PubMed Central, Emerging Sources Citation Index (Web of Science), Reference Citation Analysis, China Science and Technology Journal Database, and Superstar Journals Database. The 2023 Edition of Journal Citation Reports® cites the 2022 impact factor (IF) for *WJCO* as 2.8; IF without journal self cites: 2.8; 5-year IF: 3.0; Journal Citation Indicator: 0.36.

RESPONSIBLE EDITORS FOR THIS ISSUE

NAME OF JOURNAL
World Journal of Clinical Oncology

ISSN
ISSN 2218-4333 (online)

LAUNCH DATE
November 10, 2010

FREQUENCY
Monthly

EDITORS-IN-CHIEF
Hiten RH Patel, Stephen Safe, Jian-Hua Mao, Ken H Young

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/2218-4333/editorialboard.htm

PUBLICATION DATE
June 24, 2024

INSTRUCTIONS TO AUTHORS
https://www.wjgnet.com/bpg/gerinfo/204

GUIDELINES FOR ETHICS DOCUMENTS
https://www.wjgnet.com/bpg/GerInfo/287

GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH
https://www.wjgnet.com/bpg/gerinfo/240

PUBLICATION ETHICS
https://www.wjgnet.com/bpg/GerInfo/288

PUBLICATION MISCONDUCT
https://www.wjgnet.com/bpg/gerinfo/208

ARTICLE PROCESSING CHARGE
https://www.wjgnet.com/bpg/gerinfo/242

STEPS FOR SUBMITTING MANUSCRIPTS
https://www.wjgnet.com/bpg/GerInfo/239

ONLINE SUBMISSION
https://www.f6publishing.com

E-mail: office@baishideng.com https://www.wjgnet.com

World Journal of Clinical Oncology

Submit a Manuscript: https://www.f6publishing.com

World J Clin Oncol 2024 June 24; 15(6): 667-673

DOI: 10.5306/wjco.v15.i6.667

ISSN 2218-4333 (online)

EDITORIAL

Silica nanoparticle design for colorectal cancer treatment: Recent progress and clinical potential

Jin Meng, Zhi-Gang Wang, Xiu Zhao, Ying Wang, De-Yu Chen, De-Long Liu, Cheng-Chun Ji, Tian-Fu Wang, Li-Mei Zhang, Hai-Xia Bai, Bo-Yang Li, Yuan Liu, Lei Wang, Wei-Gang Yu, Zhi-Tao Yin

Specialty type: Oncology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification

Scientific Quality: Grade B
Novelty: Grade B
Creativity or Innovation: Grade B
Scientific Significance: Grade B

P-Reviewer: Shalaby MN, Egypt

Received: December 9, 2023
Revised: March 18, 2024
Accepted: April 24, 2024
Published online: June 24, 2024
Processing time: 197 Days and 23.6 Hours

Jin Meng, Zhi-Gang Wang, Xiu Zhao, De-Yu Chen, De-Long Liu, Cheng-Chun Ji, Tian-Fu Wang, Hai-Xia Bai, Bo-Yang Li, Yuan Liu, Lei Wang, Wei-Gang Yu, Zhi-Tao Yin, Department of Anorectal Disease, Shenyang Coloproctology Hospital, Shenyang 110000, Liaoning Province, China

Ying Wang, Acupuncture and Tuina College, Liaoning University of Traditional Chinese Medicine, Shenyang 110032, Liaoning Province, China

Li-Mei Zhang, Department of Neurology, Central Hospital of Dalian University of Technology, Dalian 116001, Liaoning Province, China

Corresponding author: Zhi-Tao Yin, MM, Chief Physician, Department of Anorectal Disease, Shenyang Coloproctology Hospital, No. 9 Nanjing North Street, Heping District, Shenyang 110000, Liaoning Province, China. yinzitao@163.com

Abstract

Colorectal cancer (CRC) is the third most common cancer worldwide and the second most common cause of cancer death. Nanotherapies are able to selectively target the delivery of cancer therapeutics, thus improving overall antitumor efficiency and reducing conventional chemotherapy side effects. Mesoporous silica nanoparticles (MSNs) have attracted the attention of many researchers due to their remarkable advantages and biosafety. We offer insights into the recent advances of MSNs in CRC treatment and their potential clinical application value.

Key Words: Colorectal cancer; Treatment; Silica nanoparticles; Mesoporous silica; Mesoporous silica nanoparticles

Core Tip: Chemotherapy is the main treatment strategy for cancer. Despite the rapid development of medicine, conventional chemotherapy has some limitations. Mesoporous silica nanoparticles (MSNs) which can increase solubility, prolong the circulation time and reduce toxicity are already in use today, and show great promise in clinical development. This is due to their favorable properties as a nanocarrier, such as high surface area, tailorable pore sizes, controllable particle sizes and shapes, and dual-functional surfaces (exterior and interior). MSNs based therapies have remarkable benefits in both *in vitro* and *in vivo* testing. These nanosystems may lead to major advances in individualized treatment and have great potential for clinical translation.

Citation: Meng J, Wang ZG, Zhao X, Wang Y, Chen DY, Liu DL, Ji CC, Wang TF, Zhang LM, Bai HX, Li BY, Liu Y, Wang L, Yu WG, Yin ZT. Silica nanoparticle design for colorectal cancer treatment: Recent progress and clinical potential. *World J Clin Oncol* 2024; 15(6): 667-673
URL: https://www.wjgnet.com/2218-4333/full/v15/i6/667.htm
DOI: https://dx.doi.org/10.5306/wjco.v15.i6.667

INTRODUCTION

Cancer is currently the leading cause of death and the single most important barrier to increased life expectancy worldwide. Colorectal cancer (CRC) is the third most common cancer worldwide and the second most common cause of cancer death. There were over 1.8 million new CRC cases and 881000 deaths in 2018[1]. CRC is the second most common cause of cancer death in the United States[2]. In addition CRC was estimated to be the second most commonly diagnosed cancer and the second leading cause of cancer death in Europe in 2020, with nearly 520000 new cases and 245000 deaths [3]. The 5-year relative survival rate for CRC ranges from 90% to 14%, and as the tumor stage increases, the 5-year relative survival rate declines. The incidence of rectal cancer and colon cancer are 67% and 63%, respectively[4].

The current options for the standard treatment of CRC include surgery, chemotherapy, radiation therapy, immunotherapy and endocrine therapy. Chemotherapy is the main treatment strategy for cancer. Despite the rapid development of medicine, conventional chemotherapy has some limitations. First, many chemotherapeutics have a short half-life or low water solubility in the body, which prevents their clinical application. Second, chemotherapeutic drugs usually lack tumor specificity, which results in undifferentiated killing of healthy cells and highly toxic side effects, and even death in extreme cases.

Nanotherapies which can increase solubility, prolong the circulation time and reduce toxicity are already in use today, and show great promise in clinical development. Among these nanoparticle platforms, mesoporous silica nanoparticles (MSNs) are a class of materials which are a focus of research. This is due to their favorable properties as a nanocarrier, such as high surface area, tailorable pore sizes, controllable particle sizes and shapes, and dual-functional surfaces (exterior and interior). Therefore, MSNs have good drug encapsulation and delivery performance[5,6].

Kresge first reported the synthesis of MSNs in the 1990s and The United States Food and Drug Administration considers silicon-based materials safe[7].

MSNs are characterized by particle sizes of 50–200 nm, pore sizes of 2–6 nm, bulk pore volume of 0.6–1 cm^3/g and a large surface area of 700–1000 m^2/g[8]. The presence of Si–OH groups on the surface allows MSNs to be functionalized using a wide variety of functional groups and allows targeted delivery to the required site of action[9].

In this review, we assess the current field of CRC therapy with mesoporous silica and offer insights into the recent advances in MSN-based targeted nanosystems in CRC treatment and their potential clinical application value (Figure 1).

MSNS IN COLORECTAL CANCER DIAGNOSIS

The prognosis of CRC patients depends on the stage of the tumor at diagnosis. The mortality rate widely differs by stage, being 8%–13% for stage I/II, 11%–47% for stage III, and almost 90% for stage IV. As the tumor stage increases, the overall survival rate declines[10].

Unfortunately, the primary diagnostic methods such as sigmoidoscopy, colonoscopy, computed tomography colonography can only detect polyps and cancers by shape/morphology. Smaller/flatter polyps are easily overlooked during routine colonoscopy, as well as nascent neoplasms with recurrent disease.

Diagnostic sensitivity can be improved to detect small/flat polyps at an early stage. Or take advantage of new molecular targeting and improve the specificity of efficient tumor diagnosis

More than half of the cancer biomarkers are glycoproteins. Specifically, changes in the composition and quantity of cell surface glycosylation-associated molecules are common features of malignant transformation and progression. Functionally, aberrant glycosylation facilitates tumor invasion, metastasis, and evasion of host immuno-surveillance. However, the content of protein glycosylation is extremely low, making the identification of glycopeptides difficult due to suppression by highly abundant non-glycopeptides. Selective enrichment is a crucial step before mass spectrometric analysis of glycoproteins. Miao *et al*[11] developed amine functionalized MSNs which were successfully used in the enrichment of N-glycoproteome in human CRC serum. Eighty-four N-linked glycosylation sites from 56 N-linked glycoproteins were identified from as little as 5 μL serum.

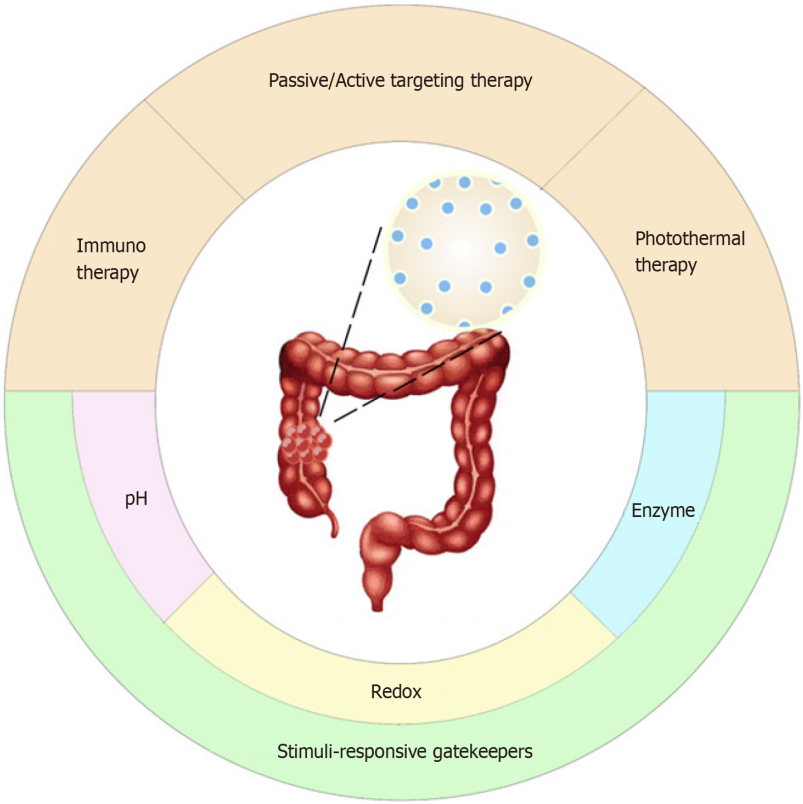


Figure 1 Mesoporous silica nanoparticle-based nanosystems for colorectal cancer therapy. These include targeted therapy, immunotherapy, photothermal therapy and some stimuli-responsive gatekeepers used in colorectal cancer treatment.

Chen *et al*[12] reported polyp-targeting, fluorescently-labeled MSNs for endoscopic detection of premalignant colonic lesions. FITC fluorescently-labeled MSNs enable fluorescence tracking both *in vitro* and *in vivo*. UEA1 (the α-L-fucose targeting lectin *Ulex europaeus* Agglutinin-1) has been shown to bind human colorectal adenocarcinomas, adenomas, and polyposis coli, but not normal epithelium. UEA1 was used for polyp-targeting, and demonstrated significant binding specificity of nanoconstructs to pathological lesions.

MSNS IN COLORECTAL CANCER THERAPY

Nanoparticle targeting cancers mainly involves three approaches: One is passive tumor targeting by utilizing the enhanced permeability and retention (EPR) of the tumor region; the second is active targeting, in which nanoparticles are functionalized on the surface of overexpressed cancer-specific ligands, thereby guiding them to tumors and cancer cells; the third is stimuli-responsive gatekeeper tumor targeting[13].

Passive targeting systems

The EPR effect has emerged as a promising therapeutic approach for cancer targeted treatment. There are already several cancer nanomedicines approved to treat solid and hematologic malignancies[14,15].

Irinotecan is a key chemotherapeutic agent for the treatment of CRC and pancreatic ductal adenocarcinoma. Despite its efficacy, irinotecan use is hindered by a high incidence of bone marrow and gastrointestinal (GI) toxicity. Liu *et al*[16] designed a PEGylation and lipid bilayer (LB) coated MSN carrier for encapsulated irinotecan delivery. LB-coated MSNs, are also known as "silicasomes". Intravenous injection of silicasomes in a well-developed orthotopic colon cancer mouse model demonstrated improved efficacy, increased survival, and reduced bone marrow and GI toxicity.

The naturally occurring polyphenol resveratrol (RES) has anticancer activity. However, the promising potential of RES is hindered by its poor aqueous solubility, which limits its biological activity. Summerlin *et al*[17] encapsulated RES in MSNs, and found that solubility increased almost two-fold and mediated *in vitro* cell death was higher than that of pure RES.

Active targeting systems

The extent of EPR effect in tumor patients has been questioned. The EPR effect in human tumors is much more complicated than in animal models. The EPR effect varies depending on cancer patients' pathological features and shows intense heterogeneity in different cancer patients with solid tumors[18,19]. Active targeting can compensate for the deficiency of EPR to improve tumor accumulation and retention. Specific ligands are conjugated to MSNs *via* surface modification. Active targeting ligands can recognize receptors expressed on the membrane of cancerous cells *via*

ligand–receptor interactions, thus improving the MSNs tumor targeting and therapeutic efficiency. The ligands could be peptides, aptamers (Apt), antibodies, proteins, saccharides, and folic acid[20]. Biomarkers on the CRC cell membrane, such as epidermal growth factor receptor (EGFR), vascular endothelial growth factors, epithelial cell adhesion molecule (EpCAM) and matrix metalloproteinases can be exploited as targets for ligand binding[21].

Active targeting drug carriers

Since first synthesized by Heidelberger and his colleagues in 1957, fluorouracil (5-FU) has been used as a component in both first-line chemotherapy regimens especially for CRC treatment and has shown good therapeutic results[22].

Chen *et al*[23] and She *et al*[24] developed hollow MSNs functionalized with epidermal growth factor (EGF) which were used as nanocarriers for 5-FU delivery to CRC cells and CRC acquired drug resistance cells, and demonstrated efficient and high specificity, and excellent targeting performance *via* the EGF–EGFR interaction.

In preclinical oncology studies and clinical trials, mifepristone (MIF) had a potent anti-proliferative effect. Gao *et al*[25] constructed MSNs conjugated with the EpCAM antibody and loaded them with MIF. The functionalized nanoparticles targeted the circulating tumor cells in mouse blood long enough to deliver MIF and inhibit CRC lung metastasis.

Active targeting genes

Gene silencing by RNA interference is a personalized field of cancer treatment. Small interfering RNAs (siRNAs) can bind to the mRNA causing site-specific cleavage and results in the silencing of specific genes responsible for cancer or other pathological conditions. At present, the ideal delivery system should be able to target cancer cells with siRNAs and release them into the cytoplasm to prevent their degradation by nucleases without adverse effects[26].

Babaei *et al*[27] constructed targeted rod-shaped MSNs for the co-delivery of survivin short hairpin RNA and camptothecin. PEGylated nanoparticles were tagged with AS1411 APt for guided transportation to CRC cells. Co-delivery of these nanoparticles significantly suppressed tumor growth rate in C26 tumor-bearing mice and improved the survival rate.

Stimuli-responsive gatekeeper targeting systems

In recent years, scientists have used the characteristics of the tumor microenvironment (TME) to design nanotargeted tumor systems. The characteristics of the TME, ATP, pH, redox reactants, hypoxia and excessive levels of certain enzyme secretions than normal tissues, are vital for tailoring stimuli-responsive targeting systems[28,29]. The pores of MSNs can be sealed with various gatekeepers and triggered by TME stimuli, which offers an opportunity to design stimuli-responsive targeting systems for controlled release.

pH-responsive gatekeeper systems

Energetic metabolism and deregulated glycolysis in cancer cells result in a high level of lactic acid and the TME has a slightly lower pH (6.5-7.2). Thus, pH-responsive nanoparticles have attracted considerable attention due to the distinct acidic features of tumor tissues compared with normal tissues[30,31].

Polydopamine pH-responsive gatekeeper

Polydopamine (PDA) can be stably coated on MSNs surface and acts as a pH-sensitive gatekeeper, controlling the selective release in the acidic tumor environment. PDA has good bio-compatibility and can be modified by various active targeting ligands containing nucleophilic functional groups (amine and thiol). These unique properties make PDA an ideal coating material[32].

DM1 is a maytansine derivative and its application in clinical cancer therapy is limited by severe side effects. Xie *et al*[33] developed MSNs loaded with DM1,PDA and EpCAM Apt. This pH targeted system is used for the treatment of CRC.

MicroRNA-155 (miR-155) is one of the most salient oncogenic microRNAs, which has been shown to regulate several cancer-related pathways and is correlated with drug resistance and genome instability. Li *et al*[34] reported on anti-miR-155-loaded MSNs surface modified with pH-sensitive PDA and AS1411 APt for the pH-responsive targeted downregulation of miR-155 for cancer therapy.

Oral pH-responsive gatekeepers

Oral chemotherapy is the most preferred route of administration in cancer treatment. Unfortunately, poor oral bioavailability limits its applications. Oral delivery systems may improve drug bioavailability by enhancing drug solubility and avoiding premature release before reaching the GI tract targeted sites. The human body naturally exhibits different pH values from the stomach (pH: 1.0–3.0) to the colon (pH: 7.0–8.0). The high variation in GI tract pH provides challenges for nanostructures[35].

Nguyen *et al*[36] loaded prednisolone into 3-aminopropyl-functionalized MSNs and coated them with succinylated ε-polylysine (SPL). The pH-responsive SPL MSNs selectively released prednisolone in the pH conditions of the colon but not in the more acidic conditions of the stomach or small intestine.

Tian *et al*[37] used the polymer poly (acrylic acid) (PAA) to anchor onto the pore channels of MSNs, which acted as a pH-responsive gatekeeper. The PAA capped MSNs exhibited a high doxorubicin (DOX) loading capacity. The DOX was protected when passing through the gastric environment and achieved targeted release in the colon.

Other pH-responsive gatekeepers

Zahiri *et al*[38] encapsulated DOX in MSNs coated with polycarboxylic acid dextran to provide pH-dependent drug release. Moreover, a CD133 RNA Apt was tagged to target CD133 overexpressed tumor cells. Narayan *et al*[39] used

chitosan as a pH-sensitive gatekeeper for the controlled release of capecitabine.

Redox-responsive gatekeeper systems

The amount of glutathione in tumor cells is approximately 10 times greater than that in normal cells. Liu *et al*[40] used a new methodology by "weaving" polyethylenimine (PEI) on the MSN surface through disulfide bonds to achieve delivery of chemotherapy (DOX) and miRNA therapy (using miRNA-145). Furthermore, an active targeting WL8 peptide (WIFPWIQL) was used to target glucose-regulated protein-78. The reducing environment hydrolyzed the disulfide bond to remove the PEI gatekeeper, resulting in the release of DOX from the carrier. This redox-responsive co-delivery system realized synergistic antitumor efficacy *in vitro* and *in vivo*, and significant anti-metastatic activity in an orthotopic colorectal tumor model.

Enzyme-responsive gatekeeper systems

Kumar *et al*[41] utilized guar gum, a natural carbohydrate polymer as an enzyme-responsive gatekeeper to load 5-FU. The release of 5-FU from capped guar gum was specifically triggered *via* colonic enzyme biodegradation.

Kumar *et al*[42] also constructed a guar gum enzyme-responsive delivery system for drug release and near-infrared (NIR) triggered photodynamic therapy.

IMMUNOTHERAPY AND PHOTOTHERMAL THERAPY

The small molecule inhibitor of the signaling hub kinase GSK3 can interfere in the PD-1/PD-L1 axis and provide effective cancer immunotherapy. Allen *et al*[43] loaded the GSK3 inhibitor AZD1080 into MSNs and coated them with a LB. Drug delivery reduced PD-1 expression and resulted in significant tumor shrinkage in mouse tumor models.

IR825 is a NIR photothermal fluorescent dye with excellent photostability and high photothermal conversion capability. However, IR825 has poor water solubility and a short metabolic half-life. Persistent luminescence nanoparticles were used as the trackable center and coated with MSNs. Wang *et al*[44] loaded IR825 and the chemotherapeutic drug irinotecan into MSNs and encapsulated them with a cancer cell-macrophage hybrid membrane. The nanoplatform produced precise combined CRC chemotherapy and image-guided photothermal therapy.

CONCLUSION

Cancer progression is a collective result of numerous pathological events. During the disease course, cancers generally become more heterogeneous and have high mutation rates. As a result of this heterogeneity, the bulk tumor may include diverse cells harboring distinct molecular signatures with differential levels of sensitivity to treatment[45]. Thus, chemotherapy alone may not produce satisfactory therapeutic results. To overcome multidrug resistance and heterogeneity, combination therapies are given which are usually complementary to chemotherapy for better therapeutic effects. MSNs can be used not only as drug delivery systems, but also as immunotherapy and photothermal nanosystems. In this review, we have shown the potential of various MSN-based nanosystems and multimodal targeting MSNs, which have demonstrated their merit over conventional therapeutic agents. These MSNs can be used for diagnosis, targeted drug therapy, targeted gene therapy, immunotherapy and photothermal therapy of CRC. Although MSN chemotherapies have shown remarkable benefits in testing, only one clinical trial on MSNs has been conducted[46]. Long-term biosafety tests deserve further study at the preclinical and clinical levels. In addition, the optimal dosage ratio of nanotherapeutic drugs requires further investigation. MSN-based nanosystems may lead to major advances in individualized treatment and have great potential for clinical translation.

FOOTNOTES

Author contributions: Yin ZT designed the study; Jin M wrote the paper; Wang ZG, Zhao X, Wang Y, Chen DY, Liu DL, Ji CC, Wang TF, Zhang LM, Ba HX, Li BY, Liu Y, Wang L, Yu WG collected and collated literature; All authors read and agreed the final manuscript.

Supported by The Natural Science Foundation of Liaoning Province, No. 2022-MS-435; and Shenyang Science and Technology Plan Project, No. 22-321-33-79.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

Country of origin: China

ORCID number: Jin Meng 0000-0002-5052-7834; Zhi-Gang Wang 0000-0002-1543-3779; Xiu Zhao 0000-0003-3790-7901; Ying Wang 0000-0003-2876-3096; De-Yu Chen 0000-0002-4651-4280; De-Long Liu 0009-0008-5212-2399; Cheng-Chun Ji 0009-0009-2735-7134; Tian-Fu Wang 0009-0007-2618-1478; Li-Mei Zhang 0009-0007-5563-2135; Hai-Xia Bai 0009-0005-6604-6065; Bo-Yang Li 0009-0007-9718-7228; Yuan Liu 0009-0008-0808-4970; Lei Wang 0000-0002-9847-5885; Wei-Gang Yu 0000-0003-3544-5889; Zhi-Tao Yin 0000-0001-9008-345X.

S-Editor: Li L
L-Editor: A
P-Editor: Zhao YQ

REFERENCES

1 **Bray F**, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018; **68**: 394-424 [PMID: 30207593 DOI: 10.3322/caac.21492]
2 **Siegel RL**, Wagle NS, Cercek A, Smith RA, Jemal A. Colorectal cancer statistics, 2023. *CA Cancer J Clin* 2023; **73**: 233-254 [PMID: 36856579 DOI: 10.3322/caac.21772]
3 **Cardoso R**, Guo F, Heisser T, Hackl M, Ihle P, De Schutter H, Van Damme N, Valerianova Z, Atanasov T, Májek O, Mužík J, Nilbert MC, Tybjerg AJ, Innos K, Mägi M, Malila N, Bouvier AM, Bouvier V, Launoy G, Woronoff AS, Cariou M, Robaszkiewicz M, Delafosse P, Poncet F, Katalinic A, Walsh PM, Senore C, Rosso S, Vincerževskienė I, Lemmens VEPP, Elferink MAG, Johannesen TB, Kørner H, Pfeffer F, Bento MJ, Rodrigues J, Alves da Costa F, Miranda A, Zadnik V, Žagar T, Lopez de Munain Marques A, Marcos-Gragera R, Puigdemont M, Galceran J, Carulla M, Chirlaque MD, Ballesta M, Sundquist K, Sundquist J, Weber M, Jordan A, Herrmann C, Mousavi M, Ryzhov A, Hoffmeister M, Brenner H. Colorectal cancer incidence, mortality, and stage distribution in European countries in the colorectal cancer screening era: an international population-based study. *Lancet Oncol* 2021; **22**: 1002-1013 [PMID: 34048685 DOI: 10.1016/S1470-2045(21)00199-6]
4 **Siegel RL**, Miller KD, Goding Sauer A, Fedewa SA, Butterly LF, Anderson JC, Cercek A, Smith RA, Jemal A. Colorectal cancer statistics, 2020. *CA Cancer J Clin* 2020; **70**: 145-164 [PMID: 32133645 DOI: 10.3322/caac.21601]
5 **Gao Y**, Gao D, Shen J, Wang Q. A Review of Mesoporous Silica Nanoparticle Delivery Systems in Chemo-Based Combination Cancer Therapies. *Front Chem* 2020; **8**: 598722 [PMID: 33330389 DOI: 10.3389/fchem.2020.598722]
6 **Sábio RM**, Meneguin AB, Ribeiro TC, Silva RR, Chorilli M. New insights towards mesoporous silica nanoparticles as a technological platform for chemotherapeutic drugs delivery. *Int J Pharm* 2019; **564**: 379-409 [PMID: 31028801 DOI: 10.1016/j.ijpharm.2019.04.067]
7 **Kresge CT**, Leonowicz ME, Roth WJ, Vartuli J, Beck J. Ordered mesoporous molecular sieves synthesized by a liquid-crystal template mechanism. *Nature* 1992; **359**: 710
8 **Castillo RR**, Vallet-Regí M. Functional Mesoporous Silica Nanocomposites: Biomedical applications and Biosafety. *Int J Mol Sci* 2019; **20** [PMID: 30791663 DOI: 10.3390/ijms20040929]
9 **Hosseinpour S**, Walsh LJ, Xu C. Biomedical application of mesoporous silica nanoparticles as delivery systems: a biological safety perspective. *J Mater Chem B* 2020; **8**: 9863-9876 [PMID: 33047764 DOI: 10.1039/d0tb01868f]
10 **Gallo G**, Vescio G, De Paola G, Sammarco G. Therapeutic Targets and Tumor Microenvironment in Colorectal Cancer. *J Clin Med* 2021; **10** [PMID: 34070480 DOI: 10.3390/jcm10112295]
11 **Miao W**, Zhang C, Cai Y, Zhang Y, Lu H. Fast solid-phase extraction of N-linked glycopeptides by amine-functionalized mesoporous silica nanoparticles. *Analyst* 2016; **141**: 2435-2440 [PMID: 27001691 DOI: 10.1039/c6an00285d]
12 **Chen NT**, Souris JS, Cheng SH, Chu CH, Wang YC, Konda V, Dougherty U, Bissonnette M, Mou CY, Chen CT, Lo LW. Lectin-functionalized mesoporous silica nanoparticles for endoscopic detection of premalignant colonic lesions. *Nanomedicine* 2017; **13**: 1941-1952 [PMID: 28363770 DOI: 10.1016/j.nano.2017.03.014]
13 **Alshehri S**, Imam SS, Rizwanullah M, Akhter S, Mahdi W, Kazi M, Ahmad J. Progress of Cancer Nanotechnology as Diagnostics, Therapeutics, and Theranostics Nanomedicine: Preclinical Promise and Translational Challenges. *Pharmaceutics* 2020; **13** [PMID: 33374391 DOI: 10.3390/pharmaceutics13010024]
14 **Maeda H**, Wu J, Sawa T, Matsumura Y, Hori K. Tumor vascular permeability and the EPR effect in macromolecular therapeutics: a review. *J Control Release* 2000; **65**: 271-284 [PMID: 10699287 DOI: 10.1016/s0168-3659(99)00248-5]
15 **Matsumura Y**, Maeda H. A new concept for macromolecular therapeutics in cancer chemotherapy: mechanism of tumoritropic accumulation of proteins and the antitumor agent smancs. *Cancer Res* 1986; **46**: 6387-6392 [PMID: 2946403]
16 **Liu X**, Jiang J, Chan R, Ji Y, Lu J, Liao YP, Okene M, Lin J, Lin P, Chang CH, Wang X, Tang I, Zheng E, Qiu W, Wainberg ZA, Nel AE, Meng H. Improved Efficacy and Reduced Toxicity Using a Custom-Designed Irinotecan-Delivering Silicasome for Orthotopic Colon Cancer. *ACS Nano* 2019; **13**: 38-53 [PMID: 30525443 DOI: 10.1021/acsnano.8b06164]
17 **Summerlin N**, Qu Z, Pujara N, Sheng Y, Jambhrunkar S, McGuckin M, Popat A. Colloidal mesoporous silica nanoparticles enhance the biological activity of resveratrol. *Colloids Surf B Biointerfaces* 2016; **144**: 1-7 [PMID: 27060664 DOI: 10.1016/j.colsurfb.2016.03.076]
18 **Shan X**, Li S, Sun B, Chen Q, Sun J, He Z, Luo C. Ferroptosis-driven nanotherapeutics for cancer treatment. *J Control Release* 2020; **319**: 322-332 [PMID: 31917296 DOI: 10.1016/j.jconrel.2020.01.008]
19 **Shi Y**, van der Meel R, Chen X, Lammers T. The EPR effect and beyond: Strategies to improve tumor targeting and cancer nanomedicine treatment efficacy. *Theranostics* 2020; **10**: 7921-7924 [PMID: 32685029 DOI: 10.7150/thno.49577]
20 **Alyassin Y**, Sayed EG, Mehta P, Ruparelia K, Arshad MS, Rasekh M, Shepherd J, Kucuk I, Wilson PB, Singh N, Chang MW, Fatouros DG, Ahmad Z. Application of mesoporous silica nanoparticles as drug delivery carriers for chemotherapeutic agents. *Drug Discov Today* 2020; **25**: 1513-1520 [PMID: 32561300 DOI: 10.1016/j.drudis.2020.06.006]
21 **Jabłońska-Trypuć A**, Matejczyk M, Rosochacki S. Matrix metalloproteinases (MMPs), the main extracellular matrix (ECM) enzymes in collagen degradation, as a target for anticancer drugs. *J Enzyme Inhib Med Chem* 2016; **31**: 177-183 [PMID: 27028474 DOI: 10.3109/14756366.2016.1161620]
22 **Hashimoto Y**, Yoshida Y, Yamada T, Aisu N, Yoshimatsu G, Yoshimura F, Hasegawa S. Current Status of Therapeutic Drug Monitoring of 5-Fluorouracil Prodrugs. *Anticancer Res* 2020; **40**: 4655-4661 [PMID: 32727789 DOI: 10.21873/anticanres.14464]

23 **Chen L**, She X, Wang T, He L, Shigdar S, Duan W, Kong L. Overcoming acquired drug resistance in colorectal cancer cells by targeted delivery of 5-FU with EGF grafted hollow mesoporous silica nanoparticles. *Nanoscale* 2015; **7**: 14080-14092 [PMID: 26242620 DOI: 10.1039/c5nr03527a]

24 **She X**, Chen L, Velleman L, Li C, Zhu H, He C, Wang T, Shigdar S, Duan W, Kong L. Fabrication of high specificity hollow mesoporous silica nanoparticles assisted by Eudragit for targeted drug delivery. *J Colloid Interface Sci* 2015; **445**: 151-160 [PMID: 25617610 DOI: 10.1016/j.jcis.2014.12.053]

25 **Gao Y**, Gu S, Zhang Y, Xie X, Yu T, Lu Y, Zhu Y, Chen W, Zhang H, Dong H, Sinko PJ, Jia L. The Architecture and Function of Monoclonal Antibody-Functionalized Mesoporous Silica Nanoparticles Loaded with Mifepristone: Repurposing Abortifacient for Cancer Metastatic Chemoprevention. *Small* 2016; **12**: 2595-2608 [PMID: 27027489 DOI: 10.1002/smll.201600550]

26 **Charbe NB**, Amnerkar ND, Ramesh B, Tambuwala MM, Bakshi HA, Aljabali AAA, Khadse SC, Satheeshkumar R, Satija S, Metha M, Chellappan DK, Shrivastava G, Gupta G, Negi P, Dua K, Zacconi FC. Small interfering RNA for cancer treatment: overcoming hurdles in delivery. *Acta Pharm Sin B* 2020; **10**: 2075-2109 [PMID: 33304780 DOI: 10.1016/j.apsb.2020.10.005]

27 **Babaei M**, Abnous K, Taghdisi SM, Taghavi S, Sh Saljooghi A, Ramezani M, Alibolandi M. Targeted rod-shaped mesoporous silica nanoparticles for the co-delivery of camptothecin and survivin shRNA in to colon adenocarcinoma in vitro and in vivo. *Eur J Pharm Biopharm* 2020; **156**: 84-96 [PMID: 32882423 DOI: 10.1016/j.ejpb.2020.08.026]

28 **Ovais M**, Mukherjee S, Pramanik A, Das D, Mukherjee A, Raza A, Chen C. Designing Stimuli-Responsive Upconversion Nanoparticles that Exploit the Tumor Microenvironment. *Adv Mater* 2020; **32**: e2000055 [PMID: 32227413 DOI: 10.1002/adma.202000055]

29 **Wu J**, Chen J, Feng Y, Tian H, Chen X. Tumor microenvironment as the "regulator" and "target" for gene therapy. *J Gene Med* 2019; **21**: e3088 [PMID: 30938916 DOI: 10.1002/jgm.3088]

30 **Webb BA**, Chimenti M, Jacobson MP, Barber DL. Dysregulated pH: a perfect storm for cancer progression. *Nat Rev Cancer* 2011; **11**: 671-677 [PMID: 21833026 DOI: 10.1038/nrc3110]

31 **Zhao T**, Huang G, Li Y, Yang S, Ramezani S, Lin Z, Wang Y, Ma X, Zeng Z, Luo M, de Boer E, Xie XJ, Thibodeaux J, Brekken RA, Sun X, Sumer BD, Gao J. A Transistor-like pH Nanoprobe for Tumour Detection and Image-guided Surgery. *Nat Biomed Eng* 2016; **1** [PMID: 28966871 DOI: 10.1038/s41551-016-0006]

32 **Cheng W**, Zeng X, Chen H, Li Z, Zeng W, Mei L, Zhao Y. Versatile Polydopamine Platforms: Synthesis and Promising Applications for Surface Modification and Advanced Nanomedicine. *ACS Nano* 2019; **13**: 8537-8565 [PMID: 31369230 DOI: 10.1021/acsnano.9b04436]

33 **Xie X**, Li F, Zhang H, Lu Y, Lian S, Lin H, Gao Y, Jia L. EpCAM aptamer-functionalized mesoporous silica nanoparticles for efficient colon cancer cell-targeted drug delivery. *Eur J Pharm Sci* 2016; **83**: 28-35 [PMID: 26690044 DOI: 10.1016/j.ejps.2015.12.014]

34 **Li Y**, Duo Y, Bi J, Zeng X, Mei L, Bao S, He L, Shan A, Zhang Y, Yu X. Targeted delivery of anti-miR-155 by functionalized mesoporous silica nanoparticles for colorectal cancer therapy. *Int J Nanomedicine* 2018; **13**: 1241-1256 [PMID: 29535520 DOI: 10.2147/IJN.S158290]

35 **Wang J**, Li Y, Nie G. Multifunctional biomolecule nanostructures for cancer therapy. *Nat Rev Mater* 2021; **6**: 766-783 [PMID: 34026278 DOI: 10.1038/s41578-021-00315-x]

36 **Nguyen CT**, Webb RI, Lambert LK, Strounina E, Lee EC, Parat MO, McGuckin MA, Popat A, Cabot PJ, Ross BP. Bifunctional Succinylated ε-Polylysine-Coated Mesoporous Silica Nanoparticles for pH-Responsive and Intracellular Drug Delivery Targeting the Colon. *ACS Appl Mater Interfaces* 2017; **9**: 9470-9483 [PMID: 28252278 DOI: 10.1021/acsami.7b00411]

37 **Tian B**, Liu S, Wu S, Lu W, Wang D, Jin L, Hu B, Li K, Wang Z, Quan Z. pH-responsive poly (acrylic acid)-gated mesoporous silica and its application in oral colon targeted drug delivery for doxorubicin. *Colloids Surf B Biointerfaces* 2017; **154**: 287-296 [PMID: 28351801 DOI: 10.1016/j.colsurfb.2017.03.024]

38 **Zahiri M**, Babaei M, Abnous K, Taghdisi SM, Ramezani M, Alibolandi M. Hybrid nanoreservoirs based on dextran-capped dendritic mesoporous silica nanoparticles for CD133-targeted drug delivery. *J Cell Physiol* 2020; **235**: 1036-1050 [PMID: 31276199 DOI: 10.1002/jcp.29019]

39 **Narayan R**, Gadag S, Cheruku SP, Raichur AM, Day CM, Garg S, Manandhar S, Pai KSR, Suresh A, Mehta CH, Nayak Y, Kumar N, Nayak UY. Chitosan-glucuronic acid conjugate coated mesoporous silica nanoparticles: A smart pH-responsive and receptor-targeted system for colorectal cancer therapy. *Carbohydr Polym* 2021; **261**: 117893 [PMID: 33766378 DOI: 10.1016/j.carbpol.2021.117893]

40 **Liu HJ**, Luan X, Feng HY, Dong X, Yang SC, Chen ZJ, Cai QY, Lu Q, Zhang Y, Sun P. Integrated combination treatment using a “smart” chemotherapy and microrna delivery system improves outcomes in an orthotopic colorectal cancer model. *Adv Funct Materi* 2018; **28**: 1801118

41 **Kumar B**, Kulanthaivel S, Mondal A, Mishra S, Banerjee B, Bhaumik A, Banerjee I, Giri S. Mesoporous silica nanoparticle based enzyme responsive system for colon specific drug delivery through guar gum capping. *Colloids Surf B Biointerfaces* 2017; **150**: 352-361 [PMID: 27847225 DOI: 10.1016/j.colsurfb.2016.10.049]

42 **Kumar B**, Murali A, Bharath AB, Giri S. Guar gum modified upconversion nanocomposites for colorectal cancer treatment through enzyme-responsive drug release and NIR-triggered photodynamic therapy. *Nanotechnology* 2019; **30**: 315102 [PMID: 30893650 DOI: 10.1088/1361-6528/ab116e]

43 **Allen SD**, Liu X, Jiang J, Liao YP, Chang CH, Nel AE, Meng H. Immune checkpoint inhibition in syngeneic mouse cancer models by a silicasome nanocarrier delivering a GSK3 inhibitor. *Biomaterials* 2021; **269**: 120635 [PMID: 33422940 DOI: 10.1016/j.biomaterials.2020.120635]

44 **Wang ZH**, Liu JM, Zhao N, Li CY, Lv SW, Hu Y, Lv H, Wang D, Wang S. Cancer Cell Macrophage Membrane Camouflaged Persistent Luminescent Nanoparticles for Imaging-Guided Photothermal Therapy of Colorectal Cancer. *ACS Appl Nano Mater* 2020; **3**: 7105 [DOI: 10.1021/acsanm.0c01433]

45 **Dagogo-Jack I**, Shaw AT. Tumour heterogeneity and resistance to cancer therapies. *Nat Rev Clin Oncol* 2018; **15**: 81-94 [PMID: 29115304 DOI: 10.1038/nrclinonc.2017.166]

46 **Lérida-Viso A**, Estepa-Fernández A, García-Fernández A, Martí-Centelles V, Martínez-Máñez R. Biosafety of mesoporous silica nanoparticles; towards clinical translation. *Adv Drug Deliv Rev* 2023; **201**: 115049 [PMID: 37573951 DOI: 10.1016/j.addr.2023.115049]

World Journal of Clinical Oncology

Submit a Manuscript: https://www.f6publishing.com

World J Clin Oncol 2024 June 24; 15(6): 674-676

DOI: 10.5306/wjco.v15.i6.674

ISSN 2218-4333 (online)

EDITORIAL

An overview of the contemporary diagnosis and management approaches for anaplastic thyroid carcinoma

Shu-Yue Zhou, Lian-Xiang Luo

Specialty type: Cell biology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single-blind

Peer-review report's classification

Scientific Quality: Grade C
Novelty: Grade C
Creativity or Innovation: Grade C
Scientific Significance: Grade B

P-Reviewer: Bondariyan N, Iran

Received: December 14, 2023
Revised: January 23, 2024
Accepted: April 18, 2024
Published online: June 24, 2024
Processing time: 193 Days and 4.3 Hours

Shu-Yue Zhou, The First Clinical College, Guangdong Medical University, Zhanjiang 524023, Guangdong Province, China

Lian-Xiang Luo, The Marine Biomedical Research Institute, Guangdong Medical University, Zhanjiang 524000, Guangdong Province, China

Corresponding author: Lian-Xiang Luo, PhD, Associate Professor, The Marine Biomedical Research Institute, Guangdong Medical University, No. 2 Wenming East Road, Xiashan District, Zhanjiang 524000, Guangdong Province, China. luolianxiang321@gdmu.edu.cn

Abstract

Thyroid carcinoma is a complex disease with several types, the most common being well-differentiated and undifferentiated. The latter, "undifferentiated carcinoma", also known as anaplastic thyroid carcinoma (ATC), is a highly aggressive malignant tumor accounting for less than 0.2% of all thyroid carcinomas and carries a poor prognosis with a median survival of 5 months. *BRAF* gene mutations are the most common molecular factor associated with this type of thyroid carcinoma. Recent advances in targeted biological agents, immunotherapy, stem cell therapy, nanotechnology, the dabrafenib/trametinib combination therapy, immune checkpoint inhibitors (ICI) and artificial intelligence offer novel treatment options. The combination therapy of dabrafenib and trametinib is the current standard treatment for patients with *BRAF-V600E* gene mutations. Besides, the dabrafenib/trametinib combination therapy, ICI, used alone or in combination with targeted therapies have raised some hopes for improving the prognosis of this deadly disease. Younger age, earlier tumor stage and radiotherapy are all prognostic factors for improved outcomes. Ultimately, therapeutic regimens should be tailored to the individual patient based on surveillance and epidemiological data, and a multidisciplinary approach is essential.

Key Words: Thyroid diseases; Thyroid cancers; Anaplastic carcinoma; Undifferentiated carcinoma; Neck mass; Aggressive malignancies

Core Tip: Anaplastic thyroid carcinoma is an infrequent but deadly form of cancer. Combining surgery, radiotherapy, chemotherapy, novel targeted therapy and immunotherapy has improved the prognosis. Multimodal management and individualized treatment with novel agents is encouraging. To further improve the outcomes, more studies shall be carried out on the molecular microenvironment and biological drivers.

Citation: Zhou SY, Luo LX. An overview of the contemporary diagnosis and management approaches for anaplastic thyroid carcinoma. *World J Clin Oncol* 2024; 15(6): 674-676
URL: https://www.wjgnet.com/2218-4333/full/v15/i6/674.htm
DOI: https://dx.doi.org/10.5306/wjco.v15.i6.674

INTRODUCTION

Although the prevalence of thyroid carcinoma is on the rise, the incidences of anaplastic thyroid carcinoma (ATC) and medullary thyroid carcinoma (MTC) remain relatively stable. Between 2000 and 2009, the overall prevalence of thyroid carcinoma experiences a significantly accelerated increase of approximately 8% per annum in both males and females[1]. ATC is a rare undifferentiated form of thyroid malignancy that accunts for a small percentage of cases, ranging from less than 0.2% to 1%-2%[2-4]. However, it is considered one of the most deadly neoplasms, with a median survival of only 4 to 6 months and a substantial decline in quality of life[3-5]. Multimodal therapy involving chemotherapy and external beam radiotherapy has shown limited success in patients with unresectable or metastatic disease, resulting in a 12-month overall survival of less than 20%. The presence of rapidly growing neck tumors often leads to severe and potentially life-threatening complications. These tumors can invade various structures, such as the trachea, leading to airway obstruction and asphyxia; the esophagus, causing dysphagia; the recurrent laryngeal nerve, resulting in paralysis and hoarseness; the major blood vessels, leading to manifestations of superior vena cava syndrome or intermittent cerebral ischemia; and the neural plexuses, causing persistent pain.

ADVANCEMENTS IN DIAGNOSIS, TREATMENT AND MANAGEMENT STRATEGIES OF ATC

An accurate diagnosis of ATC is essential and can be achieved through ultrasound and core needle biopsy. Computed tomography and magnetic resonance imaging scans can be used for staging. Molecular testing can further refine the diagnosis and reveal implicated genes, such as *BRAF-V600E* and *BRAF* wild type, which can be used to determine the optimal treatment strategy, such as anti-BRAF, anti-VEGF-A or anti-EGFR agents[6].

Nanotechnology has the potential to revolutionize drug delivery systems by enabling targeted therapy and chemo-photothermal (lenvatinib-laser irradiation) therapy. Furthermore, it may also lead to the development of magnetic or radiolabeled probes that can be used to diagnose disease progression. Moreover, the uses of an anti-programmed cell death-ligand 1 monoclonal antibody (atezolizumab) as immunotherapy may potentiate the effect of radiotherapy on malignant cells.

The initial outcomes of deep learning and artificial intelligence in the fields of diagnosis, image evaluation, treatment and outcome prediction have exhibited great potential. To ensure optimal results, it is crucial to adopt a multidisciplinary approach and formulate an individualized therapeutic regimen based on the principles outlined in surveillance, epidemiology, and end results[2,7-10].

The management protocol encompasses the established therapeutic regimen, which involves prioritizing surgical intervention, particularly debulking surgery. Additionally, adjuvant chemotherapy utilizing cisplatin or doxorubicin combined with docetaxel-paclitaxel, along with accelerated hyperfunctional external beam radiotherapy, preferably used in a neo-adjuvant and definitive manner, is a standard treatment. This therapeutic regimen has the potential to extend the median survival by approximately 10 months[6]. The novel and promising approach of utilizing targeted biological agents and immunotherapy has effectively enhanced the overall survival rates in patients who were previously considered to have a dismal prognosis[2,5,6,11,12].

The BRAF inhibitor dabrafenib and the MEK inhibitor trametinib were approved by the U.S. Food and Drug Administration in 2014 and 2018 respectively, for the treatment of mutated melanoma and mutated anaplastic thyroid carcinoma. Consequently, it has been effectively utilized in the case of metastatic or locally advanced inoperable ATC with *BRAF-V600E* gene mutation. This targeted therapy has been advised as a neoadjuvant treatment followed by surgery. It constitutes the standard treatment and guarantees a two-year overall survival rate of 80%[5,6,13,14].

The primary determinants associated with better overall outcomes have been identified as younger age, earlier tumor stage, tumor size, multifocality, utilization of radiotherapy and innovative targeted therapy[3,15].

CONCLUSION

This review assesses the understanding of highly aggressive ATC with a severe prognosis and emphasizes the signi-

ficance of accurate diagnosis and treatment. The analysis is built on the data from a broad exploration of PubMed up to September 2023, concentrating chiefly on full-text articles issued only in English within the past five years.

FOOTNOTES

Author contributions: Luo LX conceived and designed the editorial; Zhou SY wrote the editorial; Luo LX reviewed the paper and provided comments; All authors read and approved the final manuscript.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest in this article.

Country/Territory of origin: China

ORCID number: Lian-Xiang Luo 0000-0002-3391-9713.

S-Editor: Gong ZM
L-Editor: A
P-Editor: Zhao YQ

REFERENCES

1 **Shi LL**, DeSantis C, Jemal A, Chen AY. Changes in thyroid cancer incidence, post-2009 American Thyroid Association guidelines. *Laryngoscope* 2017; **127**: 2437-2441 [PMID: 28092116 DOI: 10.1002/lary.26473]
2 **Huang NS**, Shi X, Lei BW, Wei WJ, Lu ZW, Yu PC, Wang Y, Ji QH, Wang YL. An Update of the Appropriate Treatment Strategies in Anaplastic Thyroid Cancer: A Population-Based Study of 735 Patients. *Int J Endocrinol* 2019; **2019**: 8428547 [PMID: 30915116 DOI: 10.1155/2019/8428547]
3 **Xu L**, Cai L, Zhu Z, Chen G. Correction: Comparison of the cox regression to machine learning in predicting the survival of anaplastic thyroid carcinoma. *BMC Endocr Disord* 2023; **23**: 174 [PMID: 37580740 DOI: 10.1186/s12902-023-01431-1]
4 **Sugitani I**, Onoda N, Ito KI, Suzuki S. Management of Anaplastic Thyroid Carcinoma: the Fruits from the ATC Research Consortium of Japan. *J Nippon Med Sch* 2018; **85**: 18-27 [PMID: 29540641 DOI: 10.1272/jnms.2018_85-3]
5 **Califano I**, Smulever A, Jerkovich F, Pitoia F. Advances in the management of anaplastic thyroid carcinoma: transforming a life-threatening condition into a potentially treatable disease. *Rev Endocr Metab Disord* 2024; **25**: 123-147 [PMID: 37648897 DOI: 10.1007/s11154-023-09833-1]
6 **Ferrari SM**, Elia G, Ragusa F, Ruffilli I, La Motta C, Paparo SR, Patrizio A, Vita R, Benvenga S, Materazzi G, Fallahi P, Antonelli A. Novel treatments for anaplastic thyroid carcinoma. *Gland Surg* 2020; **9**: S28-S42 [PMID: 32055496 DOI: 10.21037/gs.2019.10.18]
7 **Janz TA**, Neskey DM, Nguyen SA, Lentsch EJ. Is the incidence of anaplastic thyroid cancer increasing: A population based epidemiology study. *World J Otorhinolaryngol Head Neck Surg* 2019; **5**: 34-40 [PMID: 30775700 DOI: 10.1016/j.wjorl.2018.05.006]
8 **Dong W**, Okamoto T, Ji X, Xiang J, Zhang D, Zhang P, Zhang H. Conditional Survival Rate Estimates for Anaplastic Thyroid Cancer Beyond the First Year: An Analysis of SEER Data (2004-2019). *Thyroid* 2023; **33**: 523-526 [PMID: 36329668 DOI: 10.1089/thy.2022.0339]
9 **Oliinyk D**, Augustin T, Rauch J, Koehler VF, Belka C, Spitzweg C, Käsmann L. Role of surgery to the primary tumor in metastatic anaplastic thyroid carcinoma: pooled analysis and SEER-based study. *J Cancer Res Clin Oncol* 2023; **149**: 3527-3547 [PMID: 35960373 DOI: 10.1007/s00432-022-04223-7]
10 **Cui H**, Wang R, Zhao X, Wang S, Shi X, Sang J. Development and validation of a nomogram for predicting the early death of anaplastic thyroid cancer: a SEER population-based study. *J Cancer Res Clin Oncol* 2023; **149**: 16001-16013 [PMID: 37689588 DOI: 10.1007/s00432-023-05302-z]
11 **Shaha AR**. Anaplastic Thyroid Cancer: Shifting Paradigms-A Ray of Hope. *Thyroid* 2023; **33**: 402-403 [PMID: 36856459 DOI: 10.1089/thy.2023.29150.sha]
12 **Filetti S**, Durante C, Hartl D, Leboulleux S, Locati LD, Newbold K, Papotti MG, Berruti A; ESMO Guidelines Committee. Thyroid cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†. *Ann Oncol* 2019; **30**: 1856-1883 [PMID: 31549998 DOI: 10.1093/annonc/mdz400]
13 **Gao X**, Hong C, Xie Y, Zeng X. Immunotherapy or targeted therapy: What will be the future treatment for anaplastic thyroid carcinoma? *Front Oncol* 2023; **13**: 1103147 [PMID: 37007127 DOI: 10.3389/fonc.2023.1103147]
14 **Hamidi S**, Maniakas A. Recent advances in anaplastic thyroid cancer management. *Curr Opin Endocrinol Diabetes Obes* 2023; **30**: 259-264 [PMID: 37410453 DOI: 10.1097/MED.0000000000000823]
15 **Wu SS**, Geiger JL, Scharpf J. Treatment Strategies and Tumor Characteristics and Overall Survival Among Patients With Anaplastic Thyroid Cancer-Reply. *JAMA Otolaryngol Head Neck Surg* 2023; **149**: 945-946 [PMID: 37651122 DOI: 10.1001/jamaoto.2023.2505]

World Journal of Clinical Oncology

Submit a Manuscript: https://www.f6publishing.com

World J Clin Oncol 2024 June 24; 15(6): 677-683

DOI: 10.5306/wjco.v15.i6.677

ISSN 2218-4333 (online)

EDITORIAL

Impact of sleep on gastrointestinal cancer

Joshua Lo, Pahnwat T Taweesedt, Makoto Kawai

Specialty type: Gastroenterology and hepatology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification

Scientific Quality: Grade D
Novelty: Grade B
Creativity or Innovation: Grade B
Scientific Significance: Grade C

P-Reviewer: Huang LQ, China

Received: December 27, 2023
Revised: February 8, 2024
Accepted: April 24, 2024
Published online: June 24, 2024
Processing time: 179 Days and 16.2 Hours

Joshua Lo, Department of Internal Medicine, Santa Clara Valley Medical Center, San Jose, CA 95128, United States

Pahnwat T Taweesedt, Department of Psychiatry and Behavioral Sciences, Stanford University, Stanford, CA 94305, United States

Pahnwat T Taweesedt, Makoto Kawai, Sierra Pacific Mental Illness Research, Education, and Clinical Center (MIRECC), VA Palo Alto Health Care System, Palo Alto, CA 94304, United States

Makoto Kawai, Department of Psychiatry and Behavioral Sciences, School of Medicine, Stanford University, Redwood City, CA 94063, United States

Corresponding author: Pahnwat T Taweesedt, MD, Postdoctoral Fellow, Department of Psychiatry and Behavioral Sciences, Stanford University, 401 Quarry Road, Stanford, CA 94305, United States. pahnwatt@stanford.edu

Abstract

Sleep problems have become a significant public health concern, affecting a large portion of the global population and have been linked to increased morbidity and mortality. The incidence of gastrointestinal (GI) cancers continues to rise, posing a substantial burden on healthcare systems worldwide. This editorial aims to delve into the impact of sleep on GI cancers, including esophageal, gastric, colorectal, hepatobiliary, and pancreatic cancer. Recent literature investigating the potential connections between GI cancers and sleep was reviewed. We considered aspects such as sleep duration, sleep disorders, and circadian rhythmicity, in order to explore the underlying mechanisms that can contribute to the development of GI cancers and propose avenues for future research.

Key Words: Sleep; Cancer; Gastrointestinal cancer; Esophagus; Stomach; Colon; Liver

Core Tip: Sleep problems are a growing global health concern, affecting a large population, while the rise in gastrointestinal (GI) cancers poses a significant burden on healthcare systems. This editorial explores the impact of sleep on GI cancers, reviewing up-to-date literature.

Citation: Lo J, Taweesedt PT, Kawai M. Impact of sleep on gastrointestinal cancer. *World J Clin Oncol* 2024; 15(6): 677-683
URL: https://www.wjgnet.com/2218-4333/full/v15/i6/677.htm
DOI: https://dx.doi.org/10.5306/wjco.v15.i6.677

INTRODUCTION

Sleep, the state the body requires as a process of recovery, is a vital life function that takes approximately one-third of every day. We often encounter the discussion of which is more important, quality *vs* quantity, in sleep. The simple answer is they are both important. However, it is crucial to understand that quantity and quality of sleep are closely associated. Quality of sleep means several things, including subjective feeling of rest, sleep efficiency, and normal sleep architecture (normal ratio of each sleep stage). The subjective feeling of rest is especially heavily associated with its duration. Typical sleep duration for adults ranges from six to nine hours, which is impacted by daily activities and environmental factors.

Sleep disorders encompass a wide range of conditions that disrupt normal sleep quality. The common sleep disorders, including insomnia, obstructive sleep apnea (OSA), and circadian rhythm disorders, are well known to play a role in chronic medical conditions and mental health disorders but have been understudied in cancer[1]. Commonly proposed mechanisms of cancer development, such as intermittent hypoxia, dysfunction to anti-tumor immunity, gut microbiome, and metabolic homeostasis, are also regularly discussed in the mechanism of sleep impact on medical conditions, suggesting a potential link between sleep disruption and cancers. The relationship between sleep disorders and types of cancer is still being investigated with possible bidirectional association[2,3].

There has been an increase in data supporting the relationship between sleep and various types of cancer, including breast[4], prostate[5,6], thyroid[7], lung[8], and gastrointestinal (GI) cancer[9-11]. Globally, GI cancers, such as esophageal, gastric, and hepatobiliary cancers, represent a major cause of morbidity and mortality [12]. Given the limitations in data, we were particularly intrigued by the recent study that explored the association between sleep and GI cancer[13]. While the primary mechanism of the pathophysiology between cancer and sleep disorders is not fully understood, early findings from this study indicated that sleep disorders and GI cancers, in particular, had an association around the time when the cancer diagnosis is initially made, suggesting that sleep disorders may be an early sign of cancer. In this editorial, our specific focus lies in the association between various aspects of sleep and the risk for specific GI cancers, including esophageal, gastric, hepatobiliary, and pancreatic cancer.

CURRENT INSIGHTS INTO SLEEP AND GI CANCER

The connection between inadequate sleep quality and cancer is gradually being elucidated as the multifactorial etiology of cancer is being better understood, involving cellular responses, hormonal alteration, immune function, and dietary factors.

Inflammatory, immune and cellular responses

Sleep disturbance is linked to the activation of the sympathetic nervous system, triggering inflammatory activity in human studies that can become chronic[14]. This chronic inflammation, in turn, fosters the initiation, progression, and metastasis of cancer. A landmark study in humans by Irwin *et al*[15] revealed how exposure to short sleep can quickly impact immunity against cancer, with a single night of four hours of sleep decreasing 70% of natural killer (NK) cells circulating in the immune system compared to eight hours of sleep. C-reactive protein and interleukin (IL)-6, common inflammatory markers, were associated with sleep disturbance and long sleep duration (> 8 h) whereas these markers were not associated with short sleep duration (< 7 h)[14]. In university students, the increase in IL-1 has a positive correlation with the Athens Insomnia Scale and Pittsburgh Sleep Quality Index (PSQI)[16]. What's more, chronic sleep deprivation in an animal study has also been reported to compromise the anti-tumor immune response, impacting NK cells and cytotoxic T cells[17]. In another animal model study that assessed the association between tumor growth and sleep disruption, sleep-deprived mice showed a 200% increase in the progression of tumor growth compared to the control group. Furthermore, *in vitro* study has demonstrated that chronic sleep deprivation affects the activation of macrophages, particularly M2 macrophages, that promote cancer growth[18].

Melatonin effects

Short sleep, sleep disturbance, and evening chronotype are associated with low melatonin. Melatonin is believed to have an anti-carcinogenic profile through various mechanisms, including eliminating reactive oxygen species (ROS), promoting a DNA repair system, activating NK cell function, hindering the initiation phase of tumorigenesis, and impeding the growth of cancer cell lines in humans[19]. The effects of melatonin in many types of GI cancer have been reported including esophageal cancer suppression, gastric cancer cell growth inhibition, enhancement of the efficacy of chemotherapy in hepatocellular carcinoma (HCC), colorectal cancer, and pancreatic cancer[20].

Sleep quality and quantity

For the majority of studies, the reference category for sleep duration was seven to eight hours per night. Short sleep

duration was typically defined as less than seven hours each night, while long sleep was characterized as exceeding eight hours per night[14]. Sleep fragmentation and insufficient sleep duration have been shown to amplify cortisol secretion, heighten insulin resistance, and contribute to weight gain, obesity, and diabetes each representing an independent risk factor for cancer[21,22]. Long sleep may indicate disrupted sleep continuity, impacting immune function and leading to an elevated release of pro-inflammatory cytokines as mentioned earlier. Long sleep has also been related to sedentary behavior and a less healthy lifestyle[23]. In patients with OSA, the intermittent hypoxia and disrupted sleep are believed to be the pathophysiological mechanisms that lead to upregulation of oxidative stress, hypoxia-inducible factors-1 transcription factor, ROS, vascular endothelial growth factor and DNA mutation, ultimately promoting tumor progression[24,25]. Duration of sleep has been shown in subsequent studies to impact GI cancers.

Circadian rhythm and its impact

Shift workers, especially night shift workers, are exposed to unnatural light at night, which can reduce melatonin secretion and may increase inflammatory cytokines production, circadian gene dysfunction, and impairment of DNA repair, leading to tumorigenesis. Lastly, chronotype impact on GI cancers can be linked to lifestyle, dietary, gut microbiota, and dietary factors. Individuals with a morning chronotype are more likely to have a healthier lifestyle. For example, smoking less and adhering to the Mediterranean diet in morning chronotype individuals have been associated with reduced risk of cancer[26]. On the other hand, the evening chronotype usually has poorer eating habits, potentially leading to heightened cancer risk[27]. Considering dietary factors is essential when estimating the risk of GI cancer. For gut microbiota that is associated with GI cancer, a decrease of *Alistipes* and an increased *Lachnospira* in individuals with a morning chronotype were found. The evening chronotype also exhibits higher insulin resistance and low-density lipoprotein levels, which are linked to cancer development[10].

ESOPHAGEAL CANCER

Limited research exists linking sleep factors such as sleep duration, sleep disorders, chronotypes, and their potential effects. This section explores available evidence and highlights the investigation into this specific GI malignancy.

Esophageal cancer is one of the most common types of cancer worldwide known risk factors for two types: esophageal squamous cell carcinoma (ESCC) and esophageal adenocarcinoma (EAC). Esophageal cancer has not been reported to have a significant correlation with sleep duration[28]. However, a notable association of sleep duration has been observed when classified by type of esophageal cancer. Few studies have examined the association between sleep disorders and these two types of esophageal cancer. In a prospective study that investigated sleep duration on EAC and ESCC risk in the United Kingdom Biobank, poor sleep behavior (defined as less than six hours or greater than nine hours of sleep a day and occasional daytime napping) was associated with a high risk of EAC, independent of genetic risk, but was not seen for ESCC[29].

Previous sleep disorders, including sleep apnea, insomnia, hypersomnia, circadian rhythm disorders, narcolepsy, parasomnia, sleep-related movement disorders, and unspecified sleep disorders that were found within one year of cancer diagnosis of these GI cancers, revealed a positive association with GI cancers overall, suggesting that sleep disorders may be a harbinger of GI cancers[13]. However, esophageal cancer alone failed to show a significant association with sleep disorders in subgroup analysis, which supported the findings from the propensity score matching study for participants with and without sleep disorders by Wu Zheng *et al*[30]. Moreover, there was no association between sleep symptoms such as daytime sleepiness, and snoring, with esophageal cancer both overall or within each subtype[29,31].

Concerning shift work, rotating shift male workers, known to have disruptions to circadian patterns, were found to have higher risks of esophageal cancer[32]. Surprisingly, fixed night shift work with persistent light exposure at night was not associated with esophageal cancer[32,33]. What is more, the investigation of chronotype and esophageal cancer revealed that the morning chronotype did not exhibit any apparent connection with esophageal cancer. In contrast, individuals with evening chronotype exhibited an elevated risk, specifically for ESCC, following a two-year enrollment period[13,29].

Based on the current evidence, both insufficient and excessive sleep durations may be contributing factors to EAC. The specific types of esophageal cancer should be considered when evaluating these associations. Further studies are needed to explore the impact of sleep disorders on esophageal cancer. Different types and settings of shift work as well as the types of cancer may have varying impacts on cancer risk. It is important to consider circadian preferences and disruptions, as there is potential relevance to specific types of esophageal cancer.

GASTRIC CANCER

Gastric cancer previously had a high incidence rate, but has shown a declining trend over the past several decades. Many changes to known risk factors for gastric cancers from reduction in tobacco smoking to improved sanitation, and diagnosing and treating *Helicobacter pylori*, have played an integral role in this trend. The association between sleep and gastric cancer has not been well understood, but there have been some studies to assess potential associations.

Gastric cancers are classified anatomically by location as cardia or noncardia, and histologically by type as diffuse or intestinal type, this separates types of gastric cancer into different risk profiles. Gastric cancer was investigated across five case-control studies from the Stomach Cancer Pooling Project Consortium, using stratified analysis by key factors of sex,

smoking status, socioeconomic status, anatomical site, histological type, and self-reported sleep duration[9].

Short sleep duration has been reported to be associated with gastric cancer in prior studies, this relationship was not found in this study[9,13,23,34]. However, a long sleep duration of at least nine hours was noted to be associated with gastric cancer, similar to previous studies. This relationship remained consistent whether categorized by anatomical site or histological type. Similar to esophageal cancer, gastric cancer did not exhibit a significant relationship with overall sleep disorders[13,30]. Interestingly, female adults with narcolepsy had a higher risk for gastric cancer[35]. Human leukocyte antigen haplotypes and immunological derangement in narcolepsy may be associated with cancer susceptibility. Frequent long naps were associated with an increased risk of gastric cancer and were exacerbated by night shift work[23]. However, there was no association between night shift work alone and gastric cancer[32,33]. In terms of chronotype, there was an inverse correlation between morning chronotype and gastric cancer[10] which supported the findings seen in gastroenteropancreatic neuroendocrine tumors, with lower progression and metastatic risks in the morning chronotype and higher risk in the evening chronotype[36].

While the connection between short sleep duration and gastric cancer remains unclear, a notable link can be seen with long sleep durations. Disruptions to circadian rhythm suggest increased gastric cancer risk, but the data remains controversial. Among sleep disorders, only narcolepsy exhibits a significant relationship with gastric cancer. Further studies are needed to explore the mechanisms for this association. The morning chronotype may be a protective factor for gastric cancer, aligning with patterns observed in other related tumors.

COLORECTAL CANCER

Colorectal cancer is a common and lethal cancer worldwide with the World Health Organization estimating it as the third most common diagnosed cancer and second leading cause of cancer-related death. Thus, early detection and treatment are vital. Furthermore, the relationship between sleep and colorectal cancer has been implicated relationship between sleep and colorectal cancer, further emphasizing the importance of understanding their relationship.

The evidence from a meta-analysis by Gong *et al*[19] demonstrated that long sleep duration (greater than nine or ten hours) increased the risk of colorectal cancer. A short sleep duration (less than six hours) has been linked to an increased risk of colonic adenomas development[37]. Nevertheless, neither short nor long sleep durations were associated with an elevated risk of colorectal cancer-specific mortality[38]. A sleep duration of seven to eight hours was associated with a lower risk of colorectal cancer[19]. Frequent daytime napping, occurring six to seven times per week, and extended durations exceeding 30 min, were associated with increased odds of colorectal cancer[23]. A study with the National Health Insurance Research Database of Taiwan to estimate the risk of colorectal cancer in those with sleep disorders found a significant positive association[39]. However, recent findings did not reveal a significant correlation with the overall history of sleep disorders, except if having more than five years of any sleep disorder diagnosis[13,30]. When factoring in psychiatric disorders, patients with sleep disorders and concomitant depression were found to have five times the incidence rate of colorectal cancer compared to the control group[39]. Further prospective studies are needed to prove causality. There is conflicting evidence on OSA, the most common sleep-related breathing disorder, there are conflicting evidence of OSA in the development of colorectal cancer[5,40]. Despite a non-significant relationship between OSA and colorectal cancer in a meta-analysis; subgroup analysis on studies with a follow-up period longer than five years indicated a significantly higher risk for colorectal cancer[4,41]. Adjustments for co-morbidities and variations in follow-up duration may influence the slow progression nature of the disease. Exposure to light at night may be associated with an increased risk of colorectal cancer in some studies[42]. However, similar to gastric cancer, night shift work did not show an association with colorectal cancer in meta-analysis[33]. The result for colorectal cancer outcomes in this meta-analysis displayed moderate heterogeneity, which is supported by this finding of a recent large study[32,33]. As with gastric cancer, a morning chronotype was linked to a reduced risk of colorectal cancer[10].

Suboptimal sleep durations are linked to a higher risk of colorectal cancer. Both prolonged and frequent napping carry a heightened risk for colorectal cancer. The literature shows a potential higher risk of sleep disorders in colorectal cancer with sleep disorders, but additional research with long follow-up periods is needed to establish causality in these relationships. Chronotype significantly influences colorectal cancer and could play a crucial role in preventive strategies.

HEPATOBILIARY-PANCREATIC CANCER

Hepatobiliary cancers are often common in individuals with chronic liver disease. There is very little evidence assessing the association between hepatobiliary-pancreatic cancer and sleep. This section delves into relevant research on the impact of sleep on the liver, biliary duct, and pancreatic cancer.

A prospective study of patients with advanced hepatobiliary-pancreatic cancer found that short and long durations were associated with increased mortality in the U-shape pattern[43].

This U-shape correlation pattern was found in sleep duration and incidence of HCC, hepatobiliary cancer and the mortality of HCC[44]. However, the correlation between sleep duration and individual cancer sites remains controversial. For instance, another study found a significant inverse correlation between sleep duration and HCC and hepatobiliary cancer[45]. For obese and postmenopausal patients in the United States, long sleep duration was found to be positively associated with an increased risk of liver cancer, but short sleep was not[46]. However, long duration of sleep may imply the compensation mechanism of preexisting medical conditions, including sleep disorders. Thus, it may not be the root cause of cancer genesis. Overall, there is no strong evidence suggesting a significant relationship between sleep duration

and liver or pancreatic cancer[28]. There was a positive correlation between the duration of daytime napping and both HCC and biliary tract cancer[44,45]. In a meta-analysis conducted by Wu *et al*[4], OSA was found to be associated with a higher risk for liver and pancreatic cancer. Nonetheless, recent studies have shown conflicting correlations between sleep disorders and pancreatic cancer, and no correlation has been observed in liver cancer[13,30]. Insomnia may be a risk factor for hepatobiliary cancer[45]. There was an association between a higher risk of liver cancer and the exposure to outdoor light at night or night shift[47]. Rotating shift work is associated with a decreased risk of liver cancer in Japanese men. In this study, there is no association between rotating shift work in the female gender and night shift work in both genders[32]. In contrast, rotating shift work is associated with a higher risk of biliary duct cancer[48]. In terms of chronotype, genetic liability to morningness was not associated with liver, biliary duct or pancreatic cancer in the combined analysis.

The association of sleep durations, sleep disorders, shift work and the risk of hepatobiliary-pancreatic cancer remains an area of interest, although conclusive evidence is currently lacking. The protective profile of morning chronotype against hepatobiliary-pancreatic cancer has not yet been fully elucidated, emphasizing the need for further studies to provide a more comprehensive assessment.

CLINICAL IMPLICATIONS

Lifestyle management, such as adhering to appropriate sleep durations based on age, can foster optimal development and health. For individuals with insufficient sleep duration, implementing interventions such as sleep hygiene to extend sleep duration may enhance sleep quality and potentially reduce the risk of GI cancer. Similarly, screening for underlying conditions that may lead to prolonged sleep duration, followed by appropriate treatment, might normalize sleep duration. Individuals with sleep disorders are likely to be encouraged to undergo early screening for tumor detection and treatment, adhering to established protocols, given the potential impact on GI cancer. Embracing the habits of a morning chronotype may confer health benefits, resulting in a lower risk of GI cancer. Interventions that may impact circadian rhythm and sleep quality, such as melatonin and light exposure adjustment, have been studied and may offer assistance in GI cancer treatment[20,48]. However, there is insufficient evidence to establish a clear recommendation for the interventions. More research will be required to elucidate the impact of sleep adjustments on cancer, as they may influence cancer outcomes.

CONCLUSION

Unfavorable sleep duration may increase the risk for GI cancers. Many studies indicated that an extended duration of nocturnal sleep, frequent napping, and insufficient sleep may have deleterious effects on health, increasing the risk for specific GI cancers. Future large-scale prospective studies, with additional stratification of individuals with sleep disorders and more detailed measurement of sleep duration, shift work status and chronotype, are needed to clarify the cause-effect relationship between sleep disturbances and GI cancers.

FOOTNOTES

Author contributions: Taweesedt PT conceptualized the study and finalized the manuscript; Kawai M reviewed and wrote the manuscript; Lo J wrote the manuscript and did the English language review.

Conflict-of-interest statement: The authors declare no conflict-of-interest.

Country/Territory of origin: United States

ORCID number: Pahnwat T Taweesedt 0000-0002-5791-6920; Makoto Kawai 0000-0001-9176-4388.

S-Editor: Zhang H
L-Editor: A
P-Editor: Zhao YQ

REFERENCES

1 **Grandner MA**. Sleep, Health, and Society. *Sleep Med Clin* 2020; **15**: 319-340 [PMID: 32386705 DOI: 10.1016/j.jsmc.2020.02.017]

2 **Mogavero MP**, DelRosso LM, Fanfulla F, Bruni O, Ferri R. Sleep disorders and cancer: State of the art and future perspectives. *Sleep Med Rev* 2021; **56**: 101409 [PMID: 33333427 DOI: 10.1016/j.smrv.2020.101409]

3 **Berisha A**, Shutkind K, Borniger JC. Sleep Disruption and Cancer: Chicken or the Egg? *Front Neurosci* 2022; **16**: 856235 [PMID: 35663547 DOI: 10.3389/fnins.2022.856235]

4 **Wu D**, Zhao Z, Chen C, Lu G, Wang C, Gao S, Shen J, Liu J, He J, Liang W. Impact of obstructive sleep apnea on cancer risk: a systematic review and meta-analysis. *Sleep Breath* 2023; **27**: 843-852 [PMID: 36129602 DOI: 10.1007/s11325-022-02695-y]

5 **Fang HF**, Miao NF, Chen CD, Sithole T, Chung MH. Risk of Cancer in Patients with Insomnia, Parasomnia, and Obstructive Sleep Apnea: A Nationwide Nested Case-Control Study. *J Cancer* 2015; **6**: 1140-1147 [PMID: 26516362 DOI: 10.7150/jca.12490]

6 **Sun X**, Ye D, Jiang M, Qian Y, Mao Y. Genetically proxied morning chronotype was associated with a reduced risk of prostate cancer. *Sleep* 2021; **44** [PMID: 33878190 DOI: 10.1093/sleep/zsab104]

7 **Papantoniou K**, Konrad P, Haghayegh S, Strohmaier S, Eliassen AH, Schernhammer E. Rotating Night Shift Work, Sleep, and Thyroid Cancer Risk in the Nurses' Health Study 2. *Cancers (Basel)* 2023; **15** [PMID: 38067376 DOI: 10.3390/cancers15235673]

8 **Xie J**, Zhu M, Ji M, Fan J, Huang Y, Wei X, Jiang X, Xu J, Yin R, Wang Y, Dai J, Jin G, Xu L, Hu Z, Ma H, Shen H. Relationships between sleep traits and lung cancer risk: a prospective cohort study in UK Biobank. *Sleep* 2021; **44** [PMID: 33823024 DOI: 10.1093/sleep/zsab089]

9 **Collatuzzo G**, Pelucchi C, Negri E, Kogevinas M, Huerta JM, Vioque J, de la Hera MG, Tsugane S, Shigueaki Hamada G, Hidaka A, Zhang ZF, Camargo MC, Curado MP, Lunet N, La Vecchia C, Boffetta P. Sleep Duration and Stress Level in the Risk of Gastric Cancer: A Pooled Analysis of Case-Control Studies in the Stomach Cancer Pooling (StoP) Project. *Cancers (Basel)* 2023; **15** [PMID: 37686594 DOI: 10.3390/cancers15174319]

10 **Yuan S**, Mason AM, Titova OE, Vithayathil M, Kar S, Chen J, Li X, Burgess S, Larsson SC. Morning chronotype and digestive tract cancers: Mendelian randomization study. *Int J Cancer* 2023; **152**: 697-704 [PMID: 36093575 DOI: 10.1002/ijc.34284]

11 **Büttner-Teleagă A**, Kim YT, Osel T, Richter K. Sleep Disorders in Cancer-A Systematic Review. *Int J Environ Res Public Health* 2021; **18** [PMID: 34770209 DOI: 10.3390/ijerph182111696]

12 **Sung H**, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin* 2021; **71**: 209-249 [PMID: 33538338 DOI: 10.3322/caac.21660]

13 **Loosen S**, Krieg S, Krieg A, Leyh C, Luedde T, Vetter C, Kostev K, Roderburg C. Are sleep disorders associated with the risk of gastrointestinal cancer?-A case-control study. *J Cancer Res Clin Oncol* 2023; **149**: 11369-11378 [PMID: 37378673 DOI: 10.1007/s00432-023-05009-1]

14 **Irwin MR**, Olmstead R, Carroll JE. Sleep Disturbance, Sleep Duration, and Inflammation: A Systematic Review and Meta-Analysis of Cohort Studies and Experimental Sleep Deprivation. *Biol Psychiatry* 2016; **80**: 40-52 [PMID: 26140821 DOI: 10.1016/j.biopsych.2015.05.014]

15 **Irwin M**, Mascovich A, Gillin JC, Willoughby R, Pike J, Smith TL. Partial sleep deprivation reduces natural killer cell activity in humans. *Psychosom Med* 1994; **56**: 493-498 [PMID: 7871104 DOI: 10.1097/00006842-199411000-00004]

16 **Huang J**, Song P, Hang K, Chen Z, Zhu Z, Zhang Y, Xu J, Qin J, Wang B, Qu W, Huang Z, Liang C. Sleep Deprivation Disturbs Immune Surveillance and Promotes the Progression of Hepatocellular Carcinoma. *Front Immunol* 2021; **12**: 727959 [PMID: 34539666 DOI: 10.3389/fimmu.2021.727959]

17 **Bao H**, Peng Z, Cheng X, Jian C, Li X, Shi Y, Zhu W, Hu Y, Jiang M, Song J, Fang F, Chen J, Shu X. GABA induced by sleep deprivation promotes the proliferation and migration of colon tumors through miR-223-3p endogenous pathway and exosome pathway. *J Exp Clin Cancer Res* 2023; **42**: 344 [PMID: 38105184 DOI: 10.1186/s13046-023-02921-9]

18 **Chen J**, Chen N, Huang T, Huang N, Zhuang Z, Liang H. Sleep pattern, healthy lifestyle and colorectal cancer incidence. *Sci Rep* 2022; **12**: 18317 [PMID: 36316431 DOI: 10.1038/s41598-022-21879-w]

19 **Gong YQ**, Hou FT, Xiang CL, Li CL, Hu GH, Chen CW. The mechanisms and roles of melatonin in gastrointestinal cancer. *Front Oncol* 2022; **12**: 1066698 [PMID: 36591447 DOI: 10.3389/fonc.2022.1066698]

20 **Cohn AY**, Grant LK, Nathan MD, Wiley A, Abramson M, Harder JA, Crawford S, Klerman EB, Scheer FAJL, Kaiser UB, Rahman SA, Joffe H. Effects of Sleep Fragmentation and Estradiol Decline on Cortisol in a Human Experimental Model of Menopause. *J Clin Endocrinol Metab* 2023; **108**: e1347-e1357 [PMID: 37207451 DOI: 10.1210/clinem/dgad285]

21 **Zhang SX**, Khalyfa A, Wang Y, Carreras A, Hakim F, Neel BA, Brady MJ, Qiao Z, Hirotsu C, Gozal D. Sleep fragmentation promotes NADPH oxidase 2-mediated adipose tissue inflammation leading to insulin resistance in mice. *Int J Obes (Lond)* 2014; **38**: 619-624 [PMID: 23897221 DOI: 10.1038/ijo.2013.139]

22 **Papantoniou K**, Castaño-Vinyals G, Espinosa A, Turner MC, Martín-Sánchez V, Casabonne D, Aragonés N, Gómez-Acebo I, Ardanaz E, Jimenez-Moleon JJ, Amiano P, Molina-Barceló A, Alguacil J, Fernández-Tardón G, Huerta JM, Hernández-Segura N, Perez-Gomez B, Llorca J, Vidán-Alli J, Olmedo-Requena R, Gil L, Castañon-López C, Pollan M, Kogevinas M, Moreno V. Sleep duration and napping in relation to colorectal and gastric cancer in the MCC-Spain study. *Sci Rep* 2021; **11**: 11822 [PMID: 34083698 DOI: 10.1038/s41598-021-91275-3]

23 **Gozal D**, Almendros I, Phipps AI, Campos-Rodriguez F, Martínez-García MA, Farré R. Sleep Apnoea Adverse Effects on Cancer: True, False, or Too Many Confounders? *Int J Mol Sci* 2020; **21** [PMID: 33233617 DOI: 10.3390/ijms21228779]

24 **Martinez CA**, Kerr B, Jin C, Cistulli PA, Cook KM. Obstructive Sleep Apnea Activates HIF-1 in a Hypoxia Dose-Dependent Manner in HCT116 Colorectal Carcinoma Cells. *Int J Mol Sci* 2019; **20** [PMID: 30669593 DOI: 10.3390/ijms20020445]

25 **Godos J**, Castellano S, Ferri R, Caraci F, Lanza G, Scazzina F, Alanazi AM, Marx W, Galvano F, Grosso G. Mediterranean diet and chronotype: Data from Italian adults and systematic review of observational studies. *Exp Gerontol* 2023; **181**: 112284 [PMID: 37673382 DOI: 10.1016/j.exger.2023.112284]

26 **Mortaş H**, Ayhan B, Navruz Varlı S, Köse S, Ağagündüz D, Bilici S. Rise and shine for eating right: the link between healthy nutrition and chronotype among young adults. *Front Nutr* 2023; **10**: 1285015 [PMID: 37899840 DOI: 10.3389/fnut.2023.1285015]

27 **Gu F**, Xiao Q, Chu LW, Yu K, Matthews CE, Hsing AW, Caporaso NE. Sleep Duration and Cancer in the NIH-AARP Diet and Health Study Cohort. *PLoS One* 2016; **11**: e0161561 [PMID: 27611440 DOI: 10.1371/journal.pone.0161561]

28 **Wang X**, Tian R, Zong X, Jeon MS, Luo J, Colditz GA, Wang JS, Tsilidis KK, Ju YS, Govindan R, Puri V, Cao Y. Sleep Behaviors, Genetic Predispositions, and Risk of Esophageal Cancer. *Cancer Epidemiol Biomarkers Prev* 2023; **32**: 1079-1086 [PMID: 37195052 DOI: 10.1158/1055-9965.EPI-23-0101]

29 **Wu Zheng SM**, Chen JW, Huang YM, Chen WM, Wu SY. Effect of sleep disorders on the risks of cancers and site-specific cancers. *Sleep Med* 2022; **100**: 254-261 [PMID: 36122507 DOI: 10.1016/j.sleep.2022.08.014]

30 **Li W**, Li C, Liu T, Wang Y, Ma X, Xiao X, Zhang Q, Qu J. Self-reported sleep disorders and the risk of all cancer types: evidence from the

Kailuan Cohort study. *Public Health* 2023; **223**: 209-216 [PMID: 37677850 DOI: 10.1016/j.puhe.2023.08.007]

31 **Arafa A**, Eshak ES, Iso H, Muraki I, Tamakoshi A. Night Work, Rotating Shift Work, and the Risk of Cancer in Japanese Men and Women: The JACC Study. *J Epidemiol* 2021; **31**: 585-592 [PMID: 32801280 DOI: 10.2188/jea.JE20200208]

32 **Dun A**, Zhao X, Jin X, Wei T, Gao X, Wang Y, Hou H. Association Between Night-Shift Work and Cancer Risk: Updated Systematic Review and Meta-Analysis. *Front Oncol* 2020; **10**: 1006 [PMID: 32656086 DOI: 10.3389/fonc.2020.01006]

33 **Chen Y**, Tan F, Wei L, Li X, Lyu Z, Feng X, Wen Y, Guo L, He J, Dai M, Li N. Sleep duration and the risk of cancer: a systematic review and meta-analysis including dose-response relationship. *BMC Cancer* 2018; **18**: 1149 [PMID: 30463535 DOI: 10.1186/s12885-018-5025-y]

34 **Tseng CM**, Chen YT, Tao CW, Ou SM, Hsiao YH, Li SY, Chen TJ, Perng DW, Chou KT. Adult narcoleptic patients have increased risk of cancer: A nationwide population-based study. *Cancer Epidemiol* 2015; **39**: 793-797 [PMID: 26651437 DOI: 10.1016/j.canep.2015.09.014]

35 **Barrea L**, Muscogiuri G, Pugliese G, Modica R, Laudisio D, Aprano S, Faggiano A, Colao A, Savastano S. Chronotype: what role in the context of gastroenteropancreatic neuroendocrine tumors? *J Transl Med* 2021; **19**: 324 [PMID: 34330303 DOI: 10.1186/s12967-021-03010-1]

36 **Thompson CL**, Larkin EK, Patel S, Berger NA, Redline S, Li L. Short duration of sleep increases risk of colorectal adenoma. *Cancer* 2011; **117**: 841-847 [PMID: 20936662 DOI: 10.1002/cncr.25507]

37 **Stone CR**, Haig TR, Fiest KM, McNeil J, Brenner DR, Friedenreich CM. The association between sleep duration and cancer-specific mortality: a systematic review and meta-analysis. *Cancer Causes Control* 2019; **30**: 501-525 [PMID: 30903483 DOI: 10.1007/s10552-019-01156-4]

38 **Lin CL**, Liu TC, Wang YN, Chung CH, Chien WC. The Association Between Sleep Disorders and the Risk of Colorectal Cancer in Patients: A Population-based Nested Case-Control Study. *In Vivo* 2019; **33**: 573-579 [PMID: 30804144 DOI: 10.21873/invivo.11513]

39 **Gozal D**, Ham SA, Mokhlesi B. Sleep Apnea and Cancer: Analysis of a Nationwide Population Sample. *Sleep* 2016; **39**: 1493-1500 [PMID: 27166241 DOI: 10.5665/sleep.6004]

40 **Teo YH**, Tan BKJ, Tan NKW, Yap DWT, Chai YX, Teo YN, Sia CH, Sundar R, Tan E, See A, Toh ST. Obstructive sleep apnea and the incidence and mortality of gastrointestinal cancers: a systematic review and meta-analysis of 5,120,837 participants. *J Gastrointest Oncol* 2022; **13**: 2789-2798 [PMID: 36636076 DOI: 10.21037/jgo-22-153]

41 **Garcia-Saenz A**, de Miguel AS, Espinosa A, Costas L, Aragonés N, Tonne C, Moreno V, Pérez-Gómez B, Valentin A, Pollán M, Castaño-Vinyals G, Aubé M, Kogevinas M. Association Between Outdoor Light-at-night Exposure and Colorectal Cancer in Spain. *Epidemiology* 2020; **31**: 718-727 [PMID: 32639250 DOI: 10.1097/EDE.0000000000001226]

42 **Collins KP**, Geller DA, Antoni M, Donnell DM, Tsung A, Marsh JW, Burke L, Penedo F, Terhorst L, Kamarck TW, Greene A, Buysse DJ, Steel JL. Sleep duration is associated with survival in advanced cancer patients. *Sleep Med* 2017; **32**: 208-212 [PMID: 28366336 DOI: 10.1016/j.sleep.2016.06.041]

43 **Long L**, Zhao L, Petrick JL, Liao LM, Huang T, Hakim A, Yang W, Campbell PT, Giovannucci E, McGlynn KA, Zhang X. Daytime napping, nighttime sleeping duration, and risk of hepatocellular carcinoma and liver disease-related mortality. *JHEP Rep* 2023; **5**: 100819 [PMID: 37691690 DOI: 10.1016/j.jhepr.2023.100819]

44 **Yang X**, Wang J, Wang H. Association between sleep traits and primary liver cancer: A Mendelian randomization analysis. *Eur J Clin Invest* 2023; **53**: e14002 [PMID: 37029746 DOI: 10.1111/eci.14002]

45 **Royse KE**, El-Serag HB, Chen L, White DL, Hale L, Sangi-Haghpeykar H, Jiao L. Sleep Duration and Risk of Liver Cancer in Postmenopausal Women: The Women's Health Initiative Study. *J Womens Health (Larchmt)* 2017; **26**: 1270-1277 [PMID: 28933583 DOI: 10.1089/jwh.2017.6412]

46 **Park Y**, Ramirez Y, Xiao Q, Liao LM, Jones GS, McGlynn KA. Outdoor light at night and risk of liver cancer in the NIH-AARP diet and health study. *Cancer Causes Control* 2022; **33**: 1215-1218 [PMID: 35840828 DOI: 10.1007/s10552-022-01602-w]

47 **Seeherunwong A**, Chaiear N, Khuntikeo N, Ekpanyaskul C. Cholangiocarcinoma Attributed to Occupation: A Systematic Reviews. *Asian Pac J Cancer Prev* 2022; **23**: 1837-1845 [PMID: 35763622 DOI: 10.31557/APJCP.2022.23.6.1837]

48 **Çelik A**, Usta Yeşilbalkan Ö. The Effect of the Bright White Light Application to Cancer Patients Receiving Palliative Care on Their Fatigue Level and Sleep Quality: A Randomized Control Trial. *Omega (Westport)* 2023; **88**: 303-317 [PMID: 35532064 DOI: 10.1177/00302228221093462]

World Journal of Clinical Oncology

Submit a Manuscript: https://www.f6publishing.com

World J Clin Oncol 2024 June 24; 15(6): 684-686

DOI: 10.5306/wjco.v15.i6.684

ISSN 2218-4333 (online)

EDITORIAL

Current status of anaplastic thyroid carcinoma

Abrahams Ocanto, Lisselott Torres, Felipe Couñago

Specialty type: Oncology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification

Scientific Quality: Grade C

Novelty: Grade C

Creativity or Innovation: Grade C

Scientific Significance: Grade B

P-Reviewer: Figaroa OJA, Netherlands

Received: January 11, 2024

Peer-review started: January 11, 2024

Revised: April 21, 2024

Accepted: April 25, 2024

Published online: June 24, 2024

Processing time: 165 Days and 1 Hours

Abrahams Ocanto, Lisselott Torres, Felipe Couñago, Department of Radiation Oncology, San Francisco de Asís University Hospital, Genesis Care, Madrid 28002, Spain

Abrahams Ocanto, Lisselott Torres, Felipe Couñago, Department of Radiation Oncology, Vithas La Milagrosa University Hospital, Genesis Care, Madrid 28010, Spain

Corresponding author: Abrahams Ocanto, MD, Doctor, Department of Radiation Oncology, San Francisco de Asís University Hospital, 28 Joaquín Costa St, Genesis Care, Madrid 28002, Spain. abrahams.ocanto@genesiscare.es

Abstract

In this editorial we comment on the article by Pavlidis *et al*, published in the recent issue of the *World Journal of Oncology*. We focus on the recent contributions in the management of anaplastic thyroid carcinoma, highlighting the importance of surgery and radiotherapy as first line therapies in its management and the introduction of new systemic therapies beyond chemotherapy, focused on molecular alterations, an essential step in the diagnosis and included in clinical guidelines for the selection of the ideal treatment. In contrast to other neoplasms, immunotherapy, is still beginning in studies of this pathology with encouraging results. Therefore, multimodal management of the pathology together with new drugs seems to be the logical step to increase the survival of this neoplasm.

Key Words: Anaplastic carcinoma; Thyroid diseases; Surgery; Radiotherapy; Immunotherapy

Core Tip: Anaplastic thyroid carcinoma is an entity with high mortality despite the combination of treatments, today molecular analysis opens the door to new drugs that impact survival in a positive way when used in a multimodal form.

Citation: Ocanto A, Torres L, Couñago F. Current status of anaplastic thyroid carcinoma. *World J Clin Oncol* 2024; 15(6): 684-686

URL: https://www.wjgnet.com/2218-4333/full/v15/i6/684.htm

DOI: https://dx.doi.org/10.5306/wjco.v15.i6.684

INTRODUCTION

Anaplastic thyroid cancer (ATC) is a clinical entity with a high mortality and a 5-year survival of less than 0.2%. Pavlidis *et al*[1] have performed a review of ATC, emphasizing the importance of early diagnosis and multimodal therapy to achieve the highest survival in this group of patients.

DIAGNOSIS

The initial diagnosis is the clinical presentation: Neck mass, cough, hemoptysis and dyspnea (more frequently), hoarseness and dysphagia if tracheal involvement, physical examination and ultrasound, preferably high resolution, followed by core needle biopsy; which should be prioritized over fine needle aspiration to obtain a representative sample for histopathological, genetic and molecular analysis. For both locoregional and distant staging, computed tomography angiography is preferable to magnetic resonance image. Positron emission tomography is the best option for finding occult tumor deposits. Liquid biopsy can detect malignant cells and it could contribute to diagnosis, prognosis and follow-up[1].

American thyroid association (ATA) recently integrated molecular testing in this type of tumors into its clinical guidelines, highlighting the analysis of a series of mutations involved in the aggressive evolution of these tumors and increased mortality[2], highlighting the mutation in the *RAS* gene, however, there are no approved targeted therapies that can improve the evolution of this disease. Other genes such as *BRAF*, *MET*, *NTRK* have first-line targeted therapies. With regard to the field of immunotherapy, PD-L1 expression is high in the samples analyzed, which may improve the response according to data recently published[1].

The early diagnosis in young patients (< 65 years) as well as the absence of lymph node involvement and metastasis at diagnosis, tumor size < 5 cm, are the most important prognostic factors and those that allow us to select the best treatment combination[1].

TREATMENT AND NOVEL THERAPIES

Surgery and radiotherapy have so far been shown independently to be associated with increased survival, being the corner stone, however the combination of treatments is the key, even with the advent of targeted therapies, new chemotherapy drugs and immunotherapy. Surgery according to National Comprehensive Cancer Network[2] and ATA[3] guidelines is indicated in localized cases: Lobectomy +/- thyroidectomy and lymphadenectomy. Palliative "debulky" surgery is indicated in large tumor masses and clinically significant, accompanied by adjuvant radiotherapy, chemotherapy and/or targeted therapy.

Chemotherapy, in this type of tumor there is talk of "chemoresistance", even so with the introduction of taxanes combined with platinum or anthracyclines. The combination of dabrafenib and trametinib, in *BRAF* and *MEK* gene mutation, helps to overcome this "resistance". For non-mutated gene cases, immunotherapy (anti-PD-1 and anti-PD-L1) is a new option with promising results[4].

Recently, anlotinib (tyrosine kinase inhibitor) was approved for use in combination with chemotherapy as a first-line treatment for ATC[5]. Lenvatinib, another tyrosine kinase inhibitor is used in ATC as an alternative to radioiodine and in unresectable patients as neoadjuvant therapy with increased survival. The best data continues to be provided by the combination of Dabrafenib-Trametinib when indicated. However, 5-year survival rates remain poor, immunotherapy has so far demonstrated 1-year survival rates of around 40%, and results are awaited from new treatments including oncolytic viruses, epigenetic modulators, apoptosis-inducing agents, multikinase and aurora inhibitors[1].

CONCLUSION

The management of ATC must be multimodal. The new targeted therapies as well as timing represent the change in the management of the pathology where neoadjuvant or adjuvant therapy are the novelty, however the surgery continues to be the best therapy in the initial stages of the disease. More studies and especially clinical trials directed to multimodal molecular therapy with surgery and radiotherapy are needed to optimize the results of this group of patients.

FOOTNOTES

Author contributions: Ocanto A, Torres L and Couñago F contributed to this paper; Ocanto A, Torres L and Couñago F designed the overall concept and outline of the manuscript; Couñago F contributed to the discussion and design of the manuscript; Ocanto A, Torres L and Couñago F contributed to the writing, and editing the manuscript and review of literature.

Conflict-of-interest statement: The authors declare no conflicts of interest.

Country of origin: Spain

ORCID number: Abrahams Ocanto 0000-0002-6494-8197; Felipe Couñago 0000-0001-7233-0234.

S-Editor: Qu XL
L-Editor: A
P-Editor: Zhao YQ

REFERENCES

1 **Pavlidis ET**, Galanis IN, Pavlidis TE. Update on current diagnosis and management of anaplastic thyroid carcinoma. *World J Clin Oncol* 2023; **14**: 570-583 [PMID: 38179406 DOI: 10.5306/wjco.v14.i12.570]
2 **Silver Karcioglu A**, Iwata AJ, Pusztaszeri M, Abdelhamid Ahmed AH, Randolph GW. The American Thyroid Association (ATA) integrates molecular testing into its framework for managing patients with anaplastic thyroid carcinoma (ATC): Update on the 2021 ATA ATC guidelines. *Cancer Cytopathol* 2022; **130**: 174-180 [PMID: 34618407 DOI: 10.1002/cncy.22519]
3 **Haddad RI**, Bischoff L, Ball D, Bernet V, Blomain E, Busaidy NL, Campbell M, Dickson P, Duh QY, Ehya H, Goldner WS, Guo T, Haymart M, Holt S, Hunt JP, Iagaru A, Kandeel F, Lamonica DM, Mandel S, Markovina S, McIver B, Raeburn CD, Rezaee R, Ridge JA, Roth MY, Scheri RP, Shah JP, Sipos JA, Sippel R, Sturgeon C, Wang TN, Wirth LJ, Wong RJ, Yeh M, Cassara CJ, Darlow S. Thyroid Carcinoma, Version 2.2022, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw* 2022; **20**: 925-951 [PMID: 35948029 DOI: 10.6004/jnccn.2022.0040]
4 **Saini S**, Tulla K, Maker AV, Burman KD, Prabhakar BS. Therapeutic advances in anaplastic thyroid cancer: a current perspective. *Mol Cancer* 2018; **17**: 154 [PMID: 30352606 DOI: 10.1186/s12943-018-0903-0]
5 **Zheng X**, Wang J, Ye T, Tang W, Pan X, Wang S, Liu J. Efficacy and safety of anlotinib-based chemotherapy for locally advanced or metastatic anaplastic thyroid carcinoma. *Endocrine* 2023; **81**: 540-546 [PMID: 37219702 DOI: 10.1007/s12020-023-03390-y]

World Journal of Clinical Oncology

Submit a Manuscript: https://www.f6publishing.com

World J Clin Oncol 2024 June 24; 15(6): 687-690

DOI: 10.5306/wjco.v15.i6.687

ISSN 2218-4333 (online)

EDITORIAL

New targets for cancer promotion and therapy in gliomas: Scinderin

Xi Wang, Lian-Xiang Luo

Specialty type: Oncology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification

Scientific Quality: Grade B

Novelty: Grade A

Creativity or Innovation: Grade B

Scientific Significance: Grade A

P-Reviewer: Ait Addi R, Morocco

Received: January 3, 2024

Revised: April 27, 2024

Accepted: May 20, 2024

Published online: June 24, 2024

Processing time: 173 Days and 6.5 Hours

Xi Wang, The First Clinical College, Guangdong Medical University, Zhanjiang 524023, Guangdong Province, China

Lian-Xiang Luo, The Marine Biomedical Research Institute, Guangdong Medical University, Zhanjiang 524000, Guangdong Province, China

Corresponding author: Lian-Xiang Luo, PhD, Adjunct Associate Professor, The Marine Biomedical Research Institute, Guangdong Medical University, No. 2 Wenming East Road, Zhanjiang 524000, Guangdong Province, China. luolianxiang321@gdmu.edu.cn

Abstract

Glioma is one of the most common primary intracranial tumors, characterized by invasive growth and poor prognosis. Actin cytoskeletal rearrangement is an essential event in tumor cell migration. Scinderin (SCIN), an actin severing and capping protein that regulates the actin cytoskeleton, is involved in the proliferation and migration of certain cancer cells. However, its biological role and molecular mechanism in glioma remain unclear. Lin *et al* explored the role and mechanism of SCIN in gliomas. The results showed that SCIN mechanically affected cytoskeleton remodeling and inhibited the formation of lamellipodia *via* RhoA/FAK signaling pathway. This study identifies the cancer-promoting role of SCIN and provides a potential therapeutic target for SCIN in glioma treatment.

Key Words: Glioma; Scinderin; Actin cytoskeleton; RhoA/FAK signaling; 1p/19q co-deletion

Core Tip: The role of scinderin (SCIN) in cancer progression has been studied, but its role in glioma remains unknown. Lin *et al* found that the expression level of *SCIN* mRNA was positively correlated with the tumor grade of glioma. SCIN affected cytoskeletal remodeling and inhibited lamellipodia formation through RhoA/FAK signaling pathway, thereby facilitating the migration and invasion of glioma cells.

Citation: Wang X, Luo LX. New targets for cancer promotion and therapy in gliomas: Scinderin. *World J Clin Oncol* 2024; 15(6): 687-690

URL: https://www.wjgnet.com/2218-4333/full/v15/i6/687.htm

DOI: https://dx.doi.org/10.5306/wjco.v15.i6.687

INTRODUCTION

Gliomas, tumors arising from glial cells or precursor cells, are the most common primary intracranial tumors, accounting for 26% of all primary brain and other central nervous system tumors and 81% of malignant brain tumors. Although relatively rare, they cause significant mortality and morbidity[1]. Though they are most common in the brain and glial tissue, they can arise anywhere in the central nervous system[2]. Gliomas can be categorized as Grades 1-4 based on malignant behavior, according to the fifth edition of the World Health Organization Classification of Tumors of the Central Nervous System, where Grades 1 and 2 are low-grade gliomas (LGG) and Grades 3 and 4 are high-grade gliomas [3]. 3 to 6 out of 100000 people suffer from glioma in China, the majority of which are Grades 3 and 4 gliomas [glioblastoma multiforme (GBM)]. For patients with intact brain function, surgical excision is still the preferred course of treatment. For high-grade gliomas, chemotherapy and radiation therapy come next. Glioma sufferers still have a dismal outlook, nonetheless. Thus, research into the molecular mechanisms underlying the growth of gliomas as well as the creation of novel prognostic markers and therapeutic targets are becoming increasingly important.

SCIN'S PRO-ONCOGENIC FUNCTION

An initial and fundamental step in the process of tumor metastasis is the active migration of tumor cells, which depends critically on the reorganization of the actin cytoskeleton, which drives the cellular motor signaling cascade downstream of the complex. Factors that regulate actin assembly begin to emerge as potential targets to prevent the spread and invasion of tumor cells[4]. Scinderin (SCIN), a member of the calcium-dependent gelatin superfamily, controls the tissue of actin by cutting off and capping actin. The SCIN protein consists of six homologous structural domains (*i.e.*, A1-A6). The analysis of the X-ray crystal structure indicates that calcium binding at the N-terminal end of SCIN inhibits the activation process, thereby exposing the F actin binding site on A2[5]. Prior research has documented that SCIN impacts several cellular functions, such as cancer differentiation, migration, and proliferation. For example, SCIN promotes the survival of prostate cancer cells by stabilizing epidermal growth factor receptor and MEK/ERK signaling[6]. Furthermore, filopodia formation, Cdc42 expression, and the proliferation and migration of gastric cancer cells are all inhibited by SCIN knockdown[7]. Lung cancer's progression and dissemination are likewise encouraged by SCIN[8]. Uncertainty persists regarding the molecular mechanism and biological function of SCIN in gliomas. Lin *et al*[9] were the first to investigate how SCIN works in gliomas and to search for new targets for the treatment of gliomas. Based on the GEPIA database, Lin *et al*[9] found that there was a notable increase in SCIN abundance in both LGG and GBM compared to normal tissues, and there was also an increase in SCIN expression in different types of gliomas. Recent studies have identified three particularly noteworthy molecular changes that occur early in glioma formation are prevalent in gliomas, and are tumor markers[10]. The first molecular alteration identified in gliomas is codeletion of chromosome arms 1p and 19q (1p/19q codeletion), which is believed to be associated with the diagnosis of oligodendrogliomas, greater sensitivity to chemotherapy, and better prognosis[11]. In addition, the other two are telomerase reverse transcriptase promoter mutations and indole dehydrogenase (IDH) mutations[12,13]. Mutant IDH genes have been shown to generate the proteins that change α-ketoglutarate into 2-hydroxyglutarate (2HG), a possible tumor metabolite[14]. One of the earliest known processes in the creation of gliomas has been shown to involve IDH mutations; nevertheless, the ensuing 2HG appears to promote broad epigenetic alterations, changing cellular differentiation and perhaps stimulating tumorigenesis [15]. According to Lin *et al*[9], the expression of SCIN was found to be significantly reduced in gliomas with both IDH mutations and 1p/19q chromosome co-deletion. They also observed a positive correlation between the expression level of SCIN mRNA and the tumour grade of gliomas. Lin *et al*[9] experimentally demonstrated decreased cell proliferation after silencing endogenous SCIN. Wound healing experiments demonstrated that SCIN-deficient cells migrated significantly more slowly to the scratch area than to the sh-NC group. In addition, SCIN knockdown inhibited the invasive ability of cells. The findings indicate that SCIN exerts a stimulatory influence on the migration and invasion of glioma cells. To explore this even further, Lin *et al*[9] experimentally demonstrated that SCIN prevented the RhoA/FAK signaling pathway from being activated. Interestingly, it is commonly recognized that F-actin polymerization is correlated with the inhibition of the RhoA/FAK signaling pathway, which indicates weak F-actin polymerization[16], which implies that SCIN regulates F-actin polymerization through RhoA/FAK signaling pathway. Moreover, cell motility was inhibited after the selective FAK inhibitor pf573228 and the RhoA inhibitor CCG1423SCIN were employed, indicating that SCIN promotes the malignant behavior of glioma cells through RhoA/FAK signaling pathway. In summary, lack of SCIN prevented glioma cells from proliferating, invading, and migrating. Mechanistically, SCIN blocked the RhoA/FAK signaling pathway to prevent plate foot formation and altered cytoskeletal remodeling[9]. This work establishes SCIN's pro-oncogenic function and offers a possible therapeutic target for the management of gliomas.

CONCLUSION

A correlation has been identified between the presence of wild-type IDH and an advanced tumour grade, and an elevated expression of SCIN. The absence of SCIN has been demonstrated to inhibit the development, invasion, and migration of glioma cells. Mechanistically, SCIN influences the RhoA/FAK signaling pathway, which in turn influences cytoskeletal remodeling and plate foot formation. As a possible therapeutic target for the treatment of gliomas, this study highlights the pro-oncogenic activity of SCIN.

FOOTNOTES

Author contributions: Luo LX conceived and designed the editorial, contributed to the topic selection, outline formulation, and finalization of the editorial, reviewed the paper and provided comments; Wang X wrote the editorial; and all authors read and approved the final manuscript.

Conflict-of-interest statement: The author reports no relevant conflicts of interest for this article.

Country of origin: China

ORCID number: Lian-Xiang Luo 0000-0002-3391-9713.

S-Editor: Wang JJ
L-Editor: A
P-Editor: Zhao YQ

REFERENCES

1 **Ostrom QT**, Gittleman H, Truitt G, Boscia A, Kruchko C, Barnholtz-Sloan JS. CBTRUS Statistical Report: Primary Brain and Other Central Nervous System Tumors Diagnosed in the United States in 2011-2015. *Neuro Oncol* 2018; **20**: iv1-iv86 [PMID: 30445539 DOI: 10.1093/neuonc/noy131]
2 **Ostrom QT**, Price M, Neff C, Cioffi G, Waite KA, Kruchko C, Barnholtz-Sloan JS. CBTRUS Statistical Report: Primary Brain and Other Central Nervous System Tumors Diagnosed in the United States in 2015-2019. *Neuro Oncol* 2022; **24**: v1-v95 [PMID: 36196752 DOI: 10.1093/neuonc/noac202]
3 **Louis DN**, Perry A, Wesseling P, Brat DJ, Cree IA, Figarella-Branger D, Hawkins C, Ng HK, Pfister SM, Reifenberger G, Soffietti R, von Deimling A, Ellison DW. The 2021 WHO Classification of Tumors of the Central Nervous System: a summary. *Neuro Oncol* 2021; **23**: 1231-1251 [PMID: 34185076 DOI: 10.1093/neuonc/noab106]
4 **Nürnberg A**, Kollmannsperger A, Grosse R. Pharmacological inhibition of actin assembly to target tumor cell motility. *Rev Physiol Biochem Pharmacol* 2014; **166**: 23-42 [PMID: 24193252 DOI: 10.1007/112_2013_16]
5 **Chumnarnsilpa S**, Lee WL, Nag S, Kannan B, Larsson M, Burtnick LD, Robinson RC. The crystal structure of the C-terminus of adseverin reveals the actin-binding interface. *Proc Natl Acad Sci U S A* 2009; **106**: 13719-13724 [PMID: 19666531 DOI: 10.1073/pnas.0812383106]
6 **Lai X**, Su W, Zhao H, Yang S, Zeng T, Wu W, Wang D. Loss of scinderin decreased expression of epidermal growth factor receptor and promoted apoptosis of castration-resistant prostate cancer cells. *FEBS Open Bio* 2018; **8**: 743-750 [PMID: 29744289 DOI: 10.1002/2211-5463.12412]
7 **Liu JJ**, Liu JY, Chen J, Wu YX, Yan P, Ji CD, Wang YX, Xiang DF, Zhang X, Zhang P, Cui YH, Wang JM, Bian XW, Qian F. Scinderin promotes the invasion and metastasis of gastric cancer cells and predicts the outcome of patients. *Cancer Lett* 2016; **376**: 110-117 [PMID: 27033455 DOI: 10.1016/j.canlet.2016.03.035]
8 **Liu H**, Shi D, Liu T, Yu Z, Zhou C. Lentivirus-mediated silencing of SCIN inhibits proliferation of human lung carcinoma cells. *Gene* 2015; **554**: 32-39 [PMID: 25303873 DOI: 10.1016/j.gene.2014.10.013]
9 **Lin X**, Zhao Z, Sun SP, Liu W. Scinderin promotes glioma cell migration and invasion *via* remodeling actin cytoskeleton. *World J Clin Oncol* 2024; **15**: 32-44 [PMID: 38292665 DOI: 10.5306/wjco.v15.i1.32]
10 **Eckel-Passow JE**, Lachance DH, Molinaro AM, Walsh KM, Decker PA, Sicotte H, Pekmezci M, Rice T, Kosel ML, Smirnov IV, Sarkar G, Caron AA, Kollmeyer TM, Praska CE, Chada AR, Halder C, Hansen HM, McCoy LS, Bracci PM, Marshall R, Zheng S, Reis GF, Pico AR, O'Neill BP, Buckner JC, Giannini C, Huse JT, Perry A, Tihan T, Berger MS, Chang SM, Prados MD, Wiemels J, Wiencke JK, Wrensch MR, Jenkins RB. Glioma Groups Based on 1p/19q, IDH, and TERT Promoter Mutations in Tumors. *N Engl J Med* 2015; **372**: 2499-2508 [PMID: 26061753 DOI: 10.1056/NEJMoa1407279]
11 **Fontaine D**, Vandenbos F, Lebrun C, Paquis V, Frenay M. [Diagnostic and prognostic values of 1p and 19q deletions in adult gliomas: critical review of the literature and implications in daily clinical practice]. *Rev Neurol (Paris)* 2008; **164**: 595-604 [PMID: 18565359 DOI: 10.1016/j.neurol.2008.04.002]
12 **Killela PJ**, Reitman ZJ, Jiao Y, Bettegowda C, Agrawal N, Diaz LA Jr, Friedman AH, Friedman H, Gallia GL, Giovanella BC, Grollman AP, He TC, He Y, Hruban RH, Jallo GI, Mandahl N, Meeker AK, Mertens F, Netto GJ, Rasheed BA, Riggins GJ, Rosenquist TA, Schiffman M, Shih IeM, Theodorescu D, Torbenson MS, Velculescu VE, Wang TL, Wentzensen N, Wood LD, Zhang M, McLendon RE, Bigner DD, Kinzler KW, Vogelstein B, Papadopoulos N, Yan H. TERT promoter mutations occur frequently in gliomas and a subset of tumors derived from cells with low rates of self-renewal. *Proc Natl Acad Sci U S A* 2013; **110**: 6021-6026 [PMID: 23530248 DOI: 10.1073/pnas.1303607110]
13 **Cancer Genome Atlas Research Network**, Brat DJ, Verhaak RG, Aldape KD, Yung WK, Salama SR, Cooper LA, Rheinbay E, Miller CR, Vitucci M, Morozova O, Robertson AG, Noushmehr H, Laird PW, Cherniack AD, Akbani R, Huse JT, Ciriello G, Poisson LM, Barnholtz-Sloan JS, Berger MS, Brennan C, Colen RR, Colman H, Flanders AE, Giannini C, Grifford M, Iavarone A, Jain R, Joseph I, Kim J, Kasaian K, Mikkelsen T, Murray BA, O'Neill BP, Pachter L, Parsons DW, Sougnez C, Sulman EP, Vandenberg SR, Van Meir EG, von Deimling A, Zhang H, Crain D, Lau K, Mallery D, Morris S, Paulauskis J, Penny R, Shelton T, Sherman M, Yena P, Black A, Bowen J, Dicostanzo K, Gastier-Foster J, Leraas KM, Lichtenberg TM, Pierson CR, Ramirez NC, Taylor C, Weaver S, Wise L, Zmuda E, Davidsen T, Demchok JA, Eley G, Ferguson ML, Hutter CM, Mills Shaw KR, Ozenberger BA, Sheth M, Sofia HJ, Tarnuzzer R, Wang Z, Yang L, Zenklusen JC, Ayala B, Baboud J, Chudamani S, Jensen MA, Liu J, Pihl T, Raman R, Wan Y, Wu Y, Ally A, Auman JT, Balasundaram M, Balu S, Baylin SB,

Beroukhim R, Bootwalla MS, Bowlby R, Bristow CA, Brooks D, Butterfield Y, Carlsen R, Carter S, Chin L, Chu A, Chuah E, Cibulskis K, Clarke A, Coetzee SG, Dhalla N, Fennell T, Fisher S, Gabriel S, Getz G, Gibbs R, Guin R, Hadjipanayis A, Hayes DN, Hinoue T, Hoadley K, Holt RA, Hoyle AP, Jefferys SR, Jones S, Jones CD, Kucherlapati R, Lai PH, Lander E, Lee S, Lichtenstein L, Ma Y, Maglinte DT, Mahadeshwar HS, Marra MA, Mayo M, Meng S, Meyerson ML, Mieczkowski PA, Moore RA, Mose LE, Mungall AJ, Pantazi A, Parfenov M, Park PJ, Parker JS, Perou CM, Protopopov A, Ren X, Roach J, Sabedot TS, Schein J, Schumacher SE, Seidman JG, Seth S, Shen H, Simons JV, Sipahimalani P, Soloway MG, Song X, Sun H, Tabak B, Tam A, Tan D, Tang J, Thiessen N, Triche T Jr, Van Den Berg DJ, Veluvolu U, Waring S, Weisenberger DJ, Wilkerson MD, Wong T, Wu J, Xi L, Xu AW, Zack TI, Zhang J, Aksoy BA, Arachchi H, Benz C, Bernard B, Carlin D, Cho J, DiCara D, Frazer S, Fuller GN, Gao J, Gehlenborg N, Haussler D, Heiman DI, Iype L, Jacobsen A, Ju Z, Katzman S, Kim H, Knijnenburg T, Kreisberg RB, Lawrence MS, Lee W, Leinonen K, Lin P, Ling S, Liu W, Liu Y, Lu Y, Mills G, Ng S, Noble MS, Paull E, Rao A, Reynolds S, Saksena G, Sanborn Z, Sander C, Schultz N, Senbabaoglu Y, Shen R, Shmulevich I, Sinha R, Stuart J, Sumer SO, Sun Y, Tasman N, Taylor BS, Voet D, Weinhold N, Weinstein JN, Yang D, Yoshihara K, Zheng S, Zhang W, Zou L, Abel T, Sadeghi S, Cohen ML, Eschbacher J, Hattab EM, Raghunathan A, Schniederjan MJ, Aziz D, Barnett G, Barrett W, Bigner DD, Boice L, Brewer C, Calatozzolo C, Campos B, Carlotti CG Jr, Chan TA, Cuppini L, Curley E, Cuzzubbo S, Devine K, DiMeco F, Duell R, Elder JB, Fehrenbach A, Finocchiaro G, Friedman W, Fulop J, Gardner J, Hermes B, Herold-Mende C, Jungk C, Kendler A, Lehman NL, Lipp E, Liu O, Mandt R, McGraw M, Mclendon R, McPherson C, Neder L, Nguyen P, Noss A, Nunziata R, Ostrom QT, Palmer C, Perin A, Pollo B, Potapov A, Potapova O, Rathmell WK, Rotin D, Scarpace L, Schilero C, Senecal K, Shimmel K, Shurkhay V, Sifri S, Singh R, Sloan AE, Smolenski K, Staugaitis SM, Steele R, Thorne L, Tirapelli DP, Unterberg A, Vallurupalli M, Wang Y, Warnick R, Williams F, Wolinsky Y, Bell S, Rosenberg M, Stewart C, Huang F, Grimsby JL, Radenbaugh AJ. Comprehensive, Integrative Genomic Analysis of Diffuse Lower-Grade Gliomas. *N Engl J Med* 2015; **372**: 2481-2498 [PMID: 26061751 DOI: 10.1056/NEJMoa1402121]

14 **Pirozzi CJ**, Yan H. The implications of IDH mutations for cancer development and therapy. *Nat Rev Clin Oncol* 2021; **18**: 645-661 [PMID: 34131315 DOI: 10.1038/s41571-021-00521-0]

15 **Chen R**, Smith-Cohn M, Cohen AL, Colman H. Glioma Subclassifications and Their Clinical Significance. *Neurotherapeutics* 2017; **14**: 284-297 [PMID: 28281173 DOI: 10.1007/s13311-017-0519-x]

16 **Tang J**, Kang Y, Huang L, Wu L, Peng Y. TIMP1 preserves the blood-brain barrier through interacting with CD63/integrin β 1 complex and regulating downstream FAK/RhoA signaling. *Acta Pharm Sin B* 2020; **10**: 987-1003 [PMID: 32642407 DOI: 10.1016/j.apsb.2020.02.015]

World Journal of Clinical Oncology

Submit a Manuscript: https://www.f6publishing.com

World J Clin Oncol 2024 June 24; 15(6): 691-694

DOI: 10.5306/wjco.v15.i6.691

ISSN 2218-4333 (online)

EDITORIAL

Vitamin D and prostate cancer prevention

Evita Krumina, Abrahams Ocanto, Felipe Couñago

Specialty type: Oncology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification

Scientific Quality: Grade A, Grade B, Grade D

Novelty: Grade A, Grade B, Grade B

Creativity or Innovation: Grade A, Grade B, Grade C

Scientific Significance: Grade A, Grade B, Grade C

P-Reviewer: Engida YE, Ethiopia; Gragnaniello V, Italy

Received: February 13, 2024

Revised: April 8, 2024

Accepted: May 6, 2024

Published online: June 24, 2024

Processing time: 131 Days and 10.1 Hours

Evita Krumina, Department of Radiation Oncology, GenesisCare Guadalajara, Guadalajara 19004, Spain

Abrahams Ocanto, Felipe Couñago, Department of Radiation Oncology, San Francisco de Asís University Hospital, GenesisCare Madrid, Madrid 28002, Spain

Abrahams Ocanto, Felipe Couñago, Department of Radiation Oncology, Vithas La Milagrosa University Hospital, GenesisCare Madrid, Madrid 28010, Spain

Felipe Couñago, National Director GenesisCare, Spain

Corresponding author: Abrahams Ocanto, MD, Department of Radiation Oncology, San Francisco de Asís University Hospital, Genesis Care Madrid, Madrid 28002, Spain. abraham.ocanto@gmail.com

Abstract

Vitamin D is a hot topic nowadays, especially its relationship with cancer prevention. Normally, vitamin D is associated with bone health principally, but the new research has discovered an impact on immune function and cellular signaling, even in same studies talk about a hormone, however, the most important relationship is its implication in cellular processes, inhibiting cancer growth. For now, the recent studies are oriented about a benefit and a cause-effect relationship between prostate cancer and normal levels of vitamin D. This premise opens a lot of questions in this scenario. This editorial highlighted the most important studies in this area.

Key Words: Prostate cancer; Vitamin D; Screening; Cancer; Prevention

Core Tip: This editorial remarks the importance of vitamin D beyond bone health and its relationship with prevention prostate cancer in the light of recent studies what suggests how deficiency and increased levels are related with an augmented risk of prostate cancer.

Citation: Krumina E, Ocanto A, Couñago F. Vitamin D and prostate cancer prevention. *World J Clin Oncol* 2024; 15(6): 691-694
URL: https://www.wjgnet.com/2218-4333/full/v15/i6/691.htm
DOI: https://dx.doi.org/10.5306/wjco.v15.i6.691

INTRODUCTION

According to the GLOBOCAN 2020 data, prostate cancer is the second most common cancer in men worldwide and it is also the fourth most common cancer overall. The incidence of prostate cancer is rising significantly, it is the most frequently diagnosed cancer in 112 countries and the leading cause of cancer death in 48 countries[1], accounting for more than 1.4 million cases and 396773 deaths. These numbers are expected to nearly double by 2040[2]. Furthermore, this is affecting younger men who are being diagnosed at more advanced stages of the disease. In summary, prostate cancer is a significant health problem, and early detection and proper management are critical to improving outcomes for patients. The relationship between very prevalent tumors such as prostate cancer and certain elements such as vitamin D has aroused great interest in recent days. Vitamin D serves as a precursor to the potent steroid hormone calcitriol, which regulates numerous genes that control homeostasis, epithelial cell differentiation, proliferation, and apoptosis. Low level of vitamin D is implicated in the development and progression of several diseases including bone fractures, cardiovascular disease, diabetes mellitus, and cancers[3].

VITAMIND D AND PROSTATE CANCER

Recently, Cassell and Konneh[4] in the last issue of *World Journal of Clinical Oncology* made a review about vitamin D as an essential nutrient that plays a crucial role in bone health and various body functions. Researchers have studied the possible link between vitamin D and prostate cancer. As the article indicates vitamin D possesses a potentially significant role in prostate cancer prevention, linked to its ability to influence cell proliferation, apoptosis, and angiogenesis, playing a fundamental part in immune modulation. Although no definitive cause-and-effect relationship has been established, it has been observed that adequate levels of vitamin D may be associated with a lower risk of certain cancers. There have been numerous epidemiological studies examining the relationship between vitamin D and prostate cancer, however, the evidence is mixed[5]. The findings from these studies vary, with some suggesting a potential link between higher vitamin D levels and a lower risk of developing prostate cancer, while others have not found a significant association[6,7]. The specific relationship between vitamin D and prostate cancer may vary among different populations due to factors such as sunlight exposure, genetics, dietary habits, ethnicity, and lifestyle factors.

The relationship between vitamin D and prostate cancer in the Nordic and African American populations is a topic of active research. Epidemiological studies have shown that regions with limited sun exposure, leading to decreased vitamin D synthesis, often indicate more prostate cancer incidence. A longitudinal nested case-control study conducted on Nordic men (Norway, Finland, and Sweden) has shown that both high and low levels of blood vitamin D are associated with a higher prostate cancer risk in Nordic countries. Research found that both low (< 19 nmol/L) and high (> 80 nmol/L) 25 (OH)-vitamin D serum concentrations are associated with higher prostate cancer risk. The normal average serum concentration of 25(OH)-vitamin D (40 nmol/L–60 nmol/L) comprises the lowest risk of prostate cancer[8]. Supplementing for vitamin D deficiency is recommended, but too high a serum level of vitamin D could also promote the development of cancer.

Vitamin D deficiency could be one of the reasons African American men experience more aggressive prostate cancer at a younger age compared to European American men. Vitamin D deficiency is more common in African Americans (AAs) and its deficiency is associated with advanced stage, higher tumor grade, and mortality in prostate cancer[9]. Study shows that African American prostate cancer displays quantitatively distinct vitamin D receptor (VDR) cistrome-transcriptome relationships regulated by BAZ1A. Study identified that genomic ancestry drives the VDR complex composition, genomic distribution, and transcriptional function, and is disrupted by BAZ1A and illustrates a novel driver for AA prostate cancer[10]. However, the role of vitamin D in aggressive prostate cancer in AAs is not well explored.

It is important to highlight that even in different populations there are different results that make it difficult to generate this cause-effect relationship between vitamin D and prostate cancer. Therefore, according to these studies, while vitamin D supplementation is recommended for individuals with a deficiency, it is essential to strike a balance to avoid excessive levels that could promote the development of cancer or other adverse health effects.

Cassell and Konneh[4] also explored supplementation of vitamin D in prostate cancer[4]. Do we have any guidance on vitamin D supplementation on either preventing or treating prostate cancer? Animal and cell studies have provided essential proof for a direct causal relationship between vitamin D and prostate cancer development, with data that provide solid support for the proof of principle that vitamin D signaling modulates progression through the early stages of prostate carcinogenesis and for the idea that early, life-long dietary manipulation of serum vitamin D metabolites can modify the course of early-stage prostate cancer[11].

There are several studies that have investigated the inclusion of vitamin D in the diet and the relationship of serum vitamin D levels with prostate cancer[6,12-14]. Campbell *et al*[13] with intake of vitamin D3 dose titrated to achieve serum level of 60 ng/mL founded that intensive nutritional intervention with vitamin D supplementation may benefit men on active surveillance for prostate cancer and that patients with higher initial vitamin D levels were twice as likely to have a

downward PSA slop[13]. However, there is still no definitive evidence of a beneficial effect of increasing vitamin D intake on prostate cancer risk. Therefore, there are still no specific recommendations regarding the optimal vitamin D intake to reduce the risk of prostate cancer in humans as well as to define the dose-response curve.

According to these data, the debate opens as to whether we should consider vitamin D values in all patients, even in the absence of a cause-effect mechanism, and whether it is cost-effective and sustainable for health systems. The cost-effectiveness of using vitamin D as a protective measure against prostate cancer is a complex issue and depends on several factors. The relationship between vitamin D and prostate cancer is not fully established. Some studies suggest that vitamin D may have a protective effect against prostate cancer, others have found no such association. Results strengthen the evidence that high 25(OH)D may protect against more aggressive prostate cancer[15]. Any public health intervention depends not only on its effectiveness but also on its cost. Vitamin D supplementation and food fortification are potentially effective strategies for preventing vitamin D deficiency, but their cost can be significant[16]. Additionally, measuring vitamin D levels in the entire population would also have an associated cost.

Another important topic is whether vitamin D can be used as a surrogate marker for prostate cancer screening that potentially will help predict the presence or progression of the disease. A recent study found an absence of correlation between the serum vitamin D concentration levels and prostate cancer risk[17]. There are still too few large-scale, well-conducted studies to confirm the absence of correlation. While research on the relationship between vitamin D levels and prostate cancer risk continues, it is important to note that using vitamin D levels as a sole marker for prostate cancer screening is not currently supported.

CONCLUSION

There is no evidence that vitamin D is a substitute for standard cancer treatments. The relationship between vitamin D and prostate cancer is an active area of research. Some studies suggest that vitamin D may have a protective effect against prostate cancer. However, the results are conflicting and inconsistent. In conclusion, while there are indications that vitamin D might play a role in cancer prevention, we cannot say for a definitive cause-and-effect relationship. More research is needed to better understand this connection in different populations.

FOOTNOTES

Author contributions: Krumina E, Ocanto A and Couñago F designed the overall concept and outline of the manuscript; Krumina E contributed to the discussion and design of the manuscript; Krumina E, Ocanto A and Couñago F contributed to the writing, and editing the manuscript and review of literature.

Conflict-of-interest statement: The authors declare no conflicts of interest.

Country of origin: Spain

ORCID number: Abrahams Ocanto 0000-0002-6494-8197; Felipe Couñago 0000-0001-7233-0234.

S-Editor: Che XX
L-Editor: A
P-Editor: Zhao YQ

REFERENCES

1 **Wang L**, Lu B, He M, Wang Y, Wang Z, Du L. Prostate Cancer Incidence and Mortality: Global Status and Temporal Trends in 89 Countries From 2000 to 2019. *Front Public Health* 2022; **10**: 811044 [PMID: 35252092 DOI: 10.3389/fpubh.2022.811044]
2 **Cancer Tomorrow**. Iarc.fr. [Internet] [cited 2024 Feb 10]. Available from: https://gco.iarc.fr/tomorrow/en/dataviz/tables
3 **Bahrami A**, Sahebkar A. Vitamin D as a Potential Therapeutic Option in Cancer Treatment: Is There a Role for Chemoprevention? *Anticancer Agents Med Chem* 2020; **20**: 2138-2149 [PMID: 32729431 DOI: 10.2174/1871520620999200729192728]
4 **Cassell A**, Konneh S. Unlocking the potential-vitamin D in prostate cancer prevention. *World J Clin Oncol* 2024; **15**: 169-174 [PMID: 38455136 DOI: 10.5306/wjco.v15.i2.169]
5 **La vitamina D y el cáncer**. Instituto Nacional del Cáncer. [Internet] 2023 [cited 2024 Feb 10]. Available from: https://www.cancer.gov/espanol/cancer/causas-prevencion/riesgo/dieta/hoja-informativa-vitamina-d
6 **Sobhi P**, Bahrami M, Mahdizadeh F, Fazaeli A, Babaei G, Rezagholizadeh L. Vitamin D and potential effects on cancers: a review. *Mol Biol Rep* 2024; **51**: 190 [PMID: 38270702 DOI: 10.1007/s11033-023-09111-y]
7 **Carlberg C**, Muñoz A. An update on vitamin D signaling and cancer. *Semin Cancer Biol* 2022; **79**: 217-230 [PMID: 32485310 DOI:

10.1016/j.semcancer.2020.05.018]

8 **Tuohimaa P**, Tenkanen L, Ahonen M, Lumme S, Jellum E, Hallmans G, Stattin P, Harvei S, Hakulinen T, Luostarinen T, Dillner J, Lehtinen M, Hakama M. Both high and low levels of blood vitamin D are associated with a higher prostate cancer risk: a longitudinal, nested case-control study in the Nordic countries. *Int J Cancer* 2004; **108**: 104-108 [PMID: 14618623 DOI: 10.1002/ijc.11375]

9 **Batai K**, Murphy AB, Nonn L, Kittles RA. Vitamin D and Immune Response: Implications for Prostate Cancer in African Americans. *Front Immunol* 2016; **7**: 53 [PMID: 26941739 DOI: 10.3389/fimmu.2016.00053]

10 **Siddappa M**, Hussain S, Wani SA, White J, Tang H, Gray JS, Jafari H, Wu HC, Long MD, Elhussin I, Karanam B, Wang H, Morgan R, Hardiman G, Adelani IB, Rotimi SO, Murphy AR, Nonn L, Davis MB, Kittles RA, Hughes Halbert C, Sucheston-Campbell LE, Yates C, Campbell MJ. African American Prostate Cancer Displays Quantitatively Distinct Vitamin D Receptor Cistrome-transcriptome Relationships Regulated by BAZ1A. *Cancer Res Commun* 2023; **3**: 621-639 [PMID: 37082578 DOI: 10.1158/2767-9764.CRC-22-0389]

11 **Fleet JC**, Kovalenko PL, Li Y, Smolinski J, Spees C, Yu JG, Thomas-Ahner JM, Cui M, Neme A, Carlberg C, Clinton SK. Vitamin D Signaling Suppresses Early Prostate Carcinogenesis in TgAPT(121) Mice. *Cancer Prev Res (Phila)* 2019; **12**: 343-356 [PMID: 31028080 DOI: 10.1158/1940-6207.CAPR-18-0401]

12 **Guo Z**, Huang M, Fan D, Hong Y, Zhao M, Ding R, Cheng Y, Duan S. Association between vitamin D supplementation and cancer incidence and mortality: A trial sequential meta-analysis of randomized controlled trials. *Crit Rev Food Sci Nutr* 2023; **63**: 8428-8442 [PMID: 35352965 DOI: 10.1080/10408398.2022.2056574]

13 **Campbell RA**, Li J, Malone L, Levy DA. Correlative Analysis of Vitamin D and Omega-3 Fatty Acid Intake in Men on Active Surveillance for Prostate Cancer. *Urology* 2021; **155**: 110-116 [PMID: 34144071 DOI: 10.1016/j.urology.2021.04.050]

14 **Chen QY**, Kim S, Lee B, Jeong G, Lee DH, Keum N, Manson JE, Giovannucci EL. Post-Diagnosis Vitamin D Supplement Use and Survival among Cancer Patients: A Meta-Analysis. *Nutrients* 2022; **14**: 3418 [PMID: 36014928 DOI: 10.3390/nu14163418]

15 **Gilbert R**, Martin RM, Beynon R, Harris R, Savovic J, Zuccolo L, Bekkering GE, Fraser WD, Sterne JA, Metcalfe C. Associations of circulating and dietary vitamin D with prostate cancer risk: a systematic review and dose-response meta-analysis. *Cancer Causes Control* 2011; **22**: 319-340 [PMID: 21203822 DOI: 10.1007/s10552-010-9706-3]

16 **Aguiar M**, Andronis L, Pallan M, Högler W, Frew E. Preventing vitamin D deficiency (VDD): a systematic review of economic evaluations. *Eur J Public Health* 2017; **27**: 292-301 [PMID: 28204459 DOI: 10.1093/eurpub/ckw270]

17 **Crocetto F**, Barone B, D'Aguanno G, Falcone A, de Vivo R, Rienzo M, Recchia L, Di Zazzo E. Vitamin D, a Regulator of Androgen Levels, Is Not Correlated to PSA Serum Levels in a Cohort of the Middle Italy Region Participating to a Prostate Cancer Screening Campaign. *J Clin Med* 2023; **12**: 1831 [PMID: 36902619 DOI: 10.3390/jcm12051831]

World Journal of Clinical Oncology

Submit a Manuscript: https://www.f6publishing.com

World J Clin Oncol 2024 June 24; 15(6): 695-716

DOI: 10.5306/wjco.v15.i6.695

ISSN 2218-4333 (online)

REVIEW

Gallbladder cancer: Progress in the Indian subcontinent

Ashok Kumar, Yajnadatta Sarangi, Annapurna Gupta, Aarti Sharma

Specialty type: Oncology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification

Scientific Quality: Grade B, Grade C

Novelty: Grade B, Grade C

Creativity or Innovation: Grade B, Grade C

Scientific Significance: Grade B, Grade B

P-Reviewer: Uhlmann D, Germany

Received: February 28, 2024

Revised: April 25, 2024

Accepted: May 15, 2024

Published online: June 24, 2024

Processing time: 116 Days and 19.6 Hours

Ashok Kumar, Yajnadatta Sarangi, Annapurna Gupta, Department of Surgical Gastroenterology, Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow 226014, Uttar Pradesh, India

Aarti Sharma, Division of Haematology, Mayo Clinic Arizona, Phoenix, AZ 85054, United States

Corresponding author: Ashok Kumar, FACS, FASCRS, FICS, FRCS, FRCS (Ed), MBBS, MCh, MS, Full Professor, Department of Surgical Gastroenterology, Sanjay Gandhi Post Graduate Institute of Medical Sciences, Raebareli Road, Lucknow 226014, Uttar Pradesh, India. doc.ashokgupta@gmail.com

Abstract

Gallbladder cancer (GBC) is one of the commonest biliary malignancies seen in India, Argentina, and Japan. The disease has dismal outcome as it is detected quite late due to nonspecific symptoms and signs. Early detection is the only way to improve the outcome. There have been several advances in basic as well as clinical research in the hepatobiliary and pancreatic diseases in the West and other developed countries but not enough has been done in GBC. Therefore, it is important and the responsibility of the countries with high burden of GBC to find solutions to the many unanswered questions like etiopathogenesis, early diagnosis, treatment, and prognostication. As India being one of the largest hubs for GBC in the world, it is important to know how the country has progressed on GBC. In this review, we will discuss the outcome of the publications from India highlighting the work and the developments taken place in past several decades both in basic and clinical research.

Key Words: Gallbladder cancer; India; basic research; Clinical research; Surgery; Therapeutics

Core Tip: This review is important to know the work done on gallbladder cancer from the country with high incidence of the disease and struggling to do its best. Research outcome may help to compare with the work being done in rest of the world and for the future collaborative research to find way for early diagnosis and to improve the treatment outcome of this aggressive disease.

Citation: Kumar A, Sarangi Y, Gupta A, Sharma A. Gallbladder cancer: Progress in the Indian subcontinent. *World J Clin Oncol* 2024; 15(6): 695-716
URL: https://www.wjgnet.com/2218-4333/full/v15/i6/695.htm
DOI: https://dx.doi.org/10.5306/wjco.v15.i6.695

INTRODUCTION

Gallbladder cancer (GBC) is the most common and most aggressive malignancy of the biliary tree. Early diagnosis is crucial for better prognosis of this dreaded disease. However nonspecific clinical presentations often hinder the accurate diagnosis of GBC at an early stage. GBC remains a highly lethal disease, with only 10% of all patients are upfront resectable. People diagnosed with early GBC typically have a 5-year survival rate of 30%-40%, whereas individuals with locally advanced lesions have a one-year survival rate of around 10%[1].

India carries one of the most substantial burdens of this condition, with its peak incidence among women in northern India reaching 21.5 cases per 100000 individuals. The substantial morbidity and mortality from GBC significantly hinder global cancer control efforts, particularly in high-risk populations. Currently, effective strategies to reduce GBC mortality are lacking.

Chile has the highest incidence of GBC globally, with 9.7 new cases per 100000 inhabitants each year. This is followed by Bolivia (8.1 per 100000 inhabitants), South Korea (6.5 per 100000 inhabitants), Laos (4.7 per 100000 inhabitants), and Japan (4.7 per 100000 inhabitants)[2]. In the United Kingdom, GBC accounts for less than 1% of all new cancer cases. In contrast, United States has significantly lower incidence rate compared to global trends, with rates of 1.4 per 100000 among women and 0.8 per 100000 among men.

Despite of large case load of GBC in Indian subcontinent, the extent of advancement in clinical and basic research related to the etiology, pathogenesis, diagnosis, prevention, and treatment of GBC remains unclear. This review seeks to evaluate India's progress in various aspects of GBC research and provide a comprehensive summary of GBC studies conducted across the Indian subcontinent. In this review, we have endeavored to encompass all the significant research conducted in India on GBC.

METHODOLOGY

We systematically reviewed published literature from India on gall bladder (GB) cancer between year 2000 to 2023 from online search engine PubMed and Medline using the search terms gallbladder, etiopathogenesis, prevention, Indian studies, basic research, epidemiological studies, clinical studies, and bullion operators like AND, OR, NOT. The secondary sources retrieved from these publications were identified through a manual search and assessed for relevance. Publications have been categorized in detail covering the areas of epidemiology, basic and clinical work. The result has been discussed in detail.

RESULTS

We have categorized the research published from 2000 to 2023 into five distinct areas: Demography and Etiopathogenesis, Clinicopathogenesis, Genetics and Polymorphism, Diagnostics and Imaging, Surgical Approaches and Resection, and Multimodality Therapy.

STUDIES ON DEMOGRAPHY AND ETIOPATHOGENESIS

Epidemiology

India has a high incidence of GBC and accounts for approximately 10% of the global burden of this disease. There is a pronounced regional disparity in GBC incidence across India, with considerably higher rates observed in the northern and northeastern regions compared to southern states. For instance, GBC incidence in North India (8.9/100000) is approximately 10 times greater than that in Chennai (0.8/100000). According to data from the National Cancer Registry, Delhi exhibits a similar Age-Standardized Rate (ASR) for GBC comparable to that of Chile. According to a study by Dutta *et al* [3], the ASRs for GBC in northern India and northeastern India are 11.8 per 100000 population and 17.1 per 100000 population, respectively. These rates are comparable to the high incidence areas of Bolivia (14/100000) and Chile (9.3/100000). Phadke *et al*[4] conducted a study to calculate the Annual Percentage Change (APC) in age-adjusted incidence rates of a specific health condition. They found significant APC, in the high-risk regions of Cachar [7.0 (P = 0.02)], Delhi [4.0 (P = 0.04)], and Kamrup [4.3 (P = 0.02)]. Meanwhile, in the low-risk regions of Bengaluru and Pune, the APC was 5.7 (P = 0.04) and 3.4 (P = 0.04), respectively. S *et al*[5] discovered that GB cancer incidence among women in Kamrup urban (ASR 16.2) was second highest after Chile[5]. Some epidemiological studies have also shown that, the population living in high-risk regions is associated with an elevated risk of developing GBC. Mhatre *et al*[6] from Tata Memorial Hospital

(TMH) in Mumbai conducted a study revealing demographic disparities in GBC. The study revealed 4.82-fold higher odds (95%CI: 3.87-5.99) of developing GBC among individuals born in high-risk regions compared to those born in low-risk regions. Additionally, there was a dose-response relationship observed between GBC risk and length of stay in high-risk regions, showing a lifetime exposure odds ratio (OR) of 5.58 (95%CI: 4.42-7.05) with a significant *P* value (≤ 0.001). Notably, the risk of GBC persisted even among individuals who migrated from high-risk to low-risk regions. All these studies indicate a higher disease burden of GBC in India.

Demographic risk factors

Numerous risk factors contribute to the development of GBC in Indian patients, particularly in high-risk regions, notably in the northern and northeastern states where many studies have been conducted. The Sutlej, Ganges, Yamuna, and Brahmaputra rivers, originating from glaciers in the northern Himalayas, flow east and became contaminated downstream by industrial and human waste. Several studies have explored the hypothesis that increased pollution of these rivers contributes to the risk of GBC in the North Indian population. Gupta *et al*[7] found that exposure to benzene hexachloride, dichlorodiphenyltrichloroethane, and high concentrations of cadmium in the Ganga River contribute to development of GBC. Several studies have shown an increase in *Helicobacter pylori* (*H. pylori*) and coliform counts in drinking water in the rivers mentioned above. Several studies have also shown that *Salmonella typhi* (*S. typhi*) and *H. pylori* , transmitted through fecal contamination, are linked to the development of GBC[8,9]. Evidence suggests that *Helicobacter* species may increase the risk of GBC, with ORs ranging from 2.7 to 12 in different studies from India. Tewari *et al*[10] found that *S. typhi* is significantly associated with GBC compared to gallstone disease (GSD; 33% *vs* 0%).

Many studies were conducted to find the other demographics risk factors for this dreaded disease. Mhatre *et al*[11] discovered that there is an increased risk of GBC associated with higher parity and a shorter reproductive lifespan. Same authors in another study reported that consumption of mustard oil was associated with increased risk of GBC[12]. In a gallstone-matched study, Mishra *et al*[13] identified several factors associated with GBC, notably age 50 years or older, low literacy, below-poverty-line socioeconomic status, infrequent bowel habits, history of hypertension, use of antihypertensive medications, non-vegetarian diet, cooking with firewood, consumption of hand pump water, and high coffee intake[13]. Gallstones are the most significant risk factor for GBC, present in 60%–90% of GBC patients compared to 20%–25% of an age-matched population[14]. Several studies conducted in the early 2000s explored the relationship between gallstones and GBC. Mhatre *et al*[15] identified that the presence of gallstones is associated with an elevated risk of developing GBC. Dutta *et al*[16] found that the presence of gallstones was an independent determinant associated with a younger age of patients with GBC (OR 4, 95%CI: 1.5-11; *P* = 0.006). Sharma *et al*[17] identified that the duration of symptom for gall stone disease is a significant risk factor for GBC. Conversely, Narang *et al*[18] found that ,a higher number and larger size of gallstones, along with the presence of cholesterol in gallstones, may also elevate the risk of developing GBC. Singh *et al*[19] reported that as the size of gallstones increases, there is a progression in the gallbladder mucosa response, transitioning from cholecystitis and hyperplasia to metaplasia, ultimately into carcinoma. Studies conducted in India highlighted the composition of bile and its role in gallbladder carcinoma. Sharma *et al*[19] discovered that patients with GBC had a substantial decrease in lipid species and an increase in bacterial taxa in their bile. The summary of other relevant publications on demography and etiopathogenesis is presented in Table 1[20-37].

STUDIES ON MOLECULAR PATHOGENESIS-GENETICS AND POLYMORPHISM

Our current understanding of the genetic and molecular changes associated with GBC remains limited. GBC, like other tumors, is driven by multiple genetic alterations. Several studies in India have aimed to elucidate the genetic mutations and molecular pathogenesis underlying gallbladder carcinoma. Studies from Sanjay Gandhi Postgraduate Institute of Medical Sciences, Lucknow, have identified *KRAS*, *PIK3CA*, and *EGFR* are the some of commonly mutated genes in GBC. A summary of genes related to different stages of pathogenesis is illustrated in Figure 1. Iyer *et al*[38] identified *ERBB2* alterations in early-stage GBC and proposed that anti-EGFR therapy (Afatinib) could be a promising therapeutic option. Kazmi *et al*[39] studied the role of *KRAS* and found that K-ras codon 12 mutations were highly prevalent in GBC and were associated with bad prognoses in resected GBC. Gupta *et al*[40] identified a new protein called Survivin, which was significantly associated with GBC, suggesting its role in the pathogenesis of GBC. Many studies were conducted regarding single gene expression and Global gene expression in GBC.

Studies on single gene expression

Many studies were conducted in India exploring single gene expression in GBC. Kumari *et al*[41] found that that C-erbB2 positive tumors exhibited a longer median survival compared to C-erbB2 negative tumors. Misra *et al*[42] studies p53 protein overexpression in gallbladder carcinoma. Singh and colleagues reported that MASPIN and THBS1 have an important epigenetic role in GBC[43]. Tekcham *et al*[44] identified downregulation of *PTEN* in GBC. Rai *et al*[45] found that the expression of CCKAR was significantly higher in GBC compared to GSD.

Studies on global gene expression

Several studies have also investigated global gene expression in GBC. Yadav *et al*[46] conducted a study on targeted gene sequencing of GBC and identified 184 somatic mutations and 60 germline mutations in cancer driver genes such as *SMAD4*, lysine methyltransferase 2C (*KMT2C*), and tumor protein p53. Kumari *et al*[47] used high-throughput methods and detected mutations in *P53*, *STK11*, *RICTOR*, *TSC2*, as well as *FGF3-TACC* fusion and *FGF10* amplification using next-generation sequencing platform.

Table 1 Studies on etiopathogenesis of gall bladder cancer

Serial No.	Sample size	Findings	Ref.
1	GBC (214) controls (214)	Biomass burning was recognized as a significant risk factor for GBC	Shridhar *et al*[20]
2	GBC (200); Gall stone disease (200) controls (200)	Residence in the Gangetic belt, consumption of tea, tobacco, joint family structure, chemical exposure, fried food, and high levels of secondary bile salts are risk factors of GBC	Jain *et al*[21]
3	GBC (54)	Cholelithiasis is a predisposing factor for GBC	Bhattacharjee and Nanda[22]
4	GBC (1291)	Exposure to high soil arsenic levels and proximity to river ganga are risk factors for GBC	Madhawi *et al*[23]
5	GBC (333)	Smoking, cholelithiasis, alcohol consumption, typhoid in the past, post-menopausal women are risk factors for GBC	Tyagi *et al*[24]
6	GBC (63)	Poor hygiene and water supply, malnutrition, cholelithiasis, tobacco and alcohol consumption are modifiable risk factors for GBC	Khan *et al*[25]
7	GBC (122); controls (122)	Education, intake of vitamin C, parity, and type of fuel used were significant factors for GBC	Panda *et al*[26]
8	GBC (49)	About 75% of patients diagnosed with GSD showed detectable H. pylori DNA in their gallbladder tissue	Bansal *et al*[27]
9	GSD (330)	As the stone size increases, gallbladder mucosa changes progress from cholecystitis to carcinoma	Mathur *et al*[28]
10	GBC (n = 11), Chronic cholecystitis (n = 23), Xantho-granulomatous cholecystitis (n = 11)	The cholesterol content in gallstones of GBC was significantly lower compared to that in benign gallbladder diseases	Srivastava *et al*[29]
11	GBC (390)	Chronic bacterial infection of bile is considered an etiological factor in the development of gallbladder carcinoma	Sharma *et al*[30]
12	GSD (101)	*H. pylori* colonizes regions of gastric metaplasia within the gallbladder	Misra *et al*[31]
13	GBC (328); controls (328)	Females, consumption of mustard oil, Family history, low socioeconomic status and drinking water from hand pump were the risk factors for GBC	Kumar *et al*[32]
14	GBC (27), GSD (196)	High prevalence of salmonella typhi in gall bladder carcinoma	Vaishnavi *et al*[33]
15	GBC (38)	Higher levels of biliary nitrate associated with the gallbladder carcinogenesis	Shukla *et al*[34]
16	GBC (n = 30); controls (n = 30)	Decreased levels of selenium (Se), zinc (Zn), and vitamin E are associated with an increased risk of gallbladder carcinoma	Shukla *et al*[35]
17	GBC (n = 30); controls (n = 30)	Significantly high biliary benzene hexachloride and dichloro diphenyl trichloroethane associated with gallbladder carcinogenesis	Shukla *et al*[36]
18	150 GBC	Gall stones associated with development of metaplastic, dysplastic and neoplastic mucosal changes of gall bladder mucosa	Gupta *et al*[37]

GSD: Gallstone disease; GBC: Gallbladder cancer; *H. pylori*: *Helicobacter pylori*.

Loss of heterozygosity (LOH) is frequently observed in GBC. In GBCs this change is commonly seen as the loss of one copy of a gene (heterozygous allelic loss) in multiple chromosomal regions. This phenomenon has been extensively studied and is known as LOH. Priya *et al*[48] observed LOH in *FHIT* gene. Jain *et al*[49] detected LOH at 8 Loci, that is 3p12, 3p14.2, 5q21, 9p21, 9q, 13q, 17p13, and 18q for tumor suppressor genes (*DUTT1*, *FHIT*, *APC*, *p16*, *FCMD*, *RB1*, *p53*, and *DCC* genes). There are few studies that examined the aberrant promoter methylation gene. Pandey *et al*[50] from Lucknow studied candidate genes and identified *GSTT1, NAT2, APOB,* and *MTHFR* mutations. Numerous other studies on genetics and polymorphisms have been published, and some of them are summarized in Table 2[51-93].

STUDIES ON CLINICOPATHOLOGICAL ASPECT OF GBC

In this section, we have described clinicopathological parameters including presenting symptoms, screening methods, histopathological findings, prognostic factors, and tumor characteristics.

Symptomatology

Patients with GBC typically present with pain in the right upper quadrant and epigastrium region of the abdomen, with or without changes in the character of the pain. They may also exhibit symptoms such as jaundice, features of GOO

Table 2 Studies on genetics and polymorphism in gall bladder cancer

Serial No.	Sample size	Findings	Ref.
1	-	IGF-MAPK cascade, p38 MAPK pathway, p53 pathway, and FAS signaling pathway as highly enriched among dysregulated miRNAs in GBC	Saxena *et al*[51]
2	-	*PARP1 rs1136410* (A/G) associated with early onset of GBC	Anjali *et al*[52]
3	GBC (29), controls (29)	*VEGF-A* expression can be used as potential prognostic biomarker in GBC	Singh *et al*[53]
4	-	Studied the prognostic significance of the oxidative stress marker 8-OH-dG and genes associated with the BER pathway	Singh *et al*[54]
5	GBC (25)	In gallbladder cancer patients, mutations were identified in both P53 and codon 12 of KRAS	Shukla *et al*[55]
6	-	Mutations in the sorcin gene associated with poor overall survival in GBC	Shabnam *et al*[56]
7	GBC (523), controls (274)	Studied the *TERT-CLPTM1L* and *8q24* Genetic Variants in GBC	Yadav *et al*[57]
8	GBC (50)	Individual and repetitive mutations of shh gene in GBC can be used as diagnostic marker	Dixit *et al*[58]
9	GBC (50)	Overexpression of Her2/neu and Ki67 in gallbladder cancer associated with lymph node metastasis	Pujani *et al*[59]
10	GBC (541), controls (307)	*KRAS rs61764370* polymorphism is significantly associated with GBC	Kazmi *et al*[60]
11	-	Studied Epigenetic silencing of *APC* in advanced GBC.	Tekcham *et al*[61]
12	GBC (24)	Found 7 hypermethylated or down-regulated (*e.g.*, *FBN1*, *LPP*, and *SOD3*) and 61 hypomethylated or up-regulated markers (*e.g.*, *HBE1*, *SNRPF*, *TPD52*) for GBC	Sharma *et al*[62]
13	Cases (50)	The level of *EGFR* expression correlates with the aggressiveness of the disease	Kumar *et al*[63]
14	GBC (52)	Tγδ17 could serve as a potential predictive biomarker in GBC	Patil *et al*[64]
15	GBC (30)	The *MTHFR A1298C* polymorphism associated with development of GBC	Dixit *et al*[65]
16	GBC (37)	Telomere dysfunction and alterations are the earlier events in progression of GBC	Poojary *et al*[66]
17	GBC (148), controls (256)	*CYP-17* gene polymorphism is associated with risk of gallbladder cancer	Dwivedi *et al*[67]
18	-	*LXR-β* polymorphisms associated with GBC	Sharma *et al*[68]
19	GBC (195), controls (300)	Vascular endothelial growth factor single nucleotide polymorphism associated with GBC	Mishra *et al*[69]
20	GBC (35)	mitochondrial D-loop mutation associated with GBC	Maurya *et al*[70]
21	GBC (410), controls (210)	Estrogen and progesterone receptor sequence associated with increased risk of *GBC*	Srivastava *et al*[71]
22	-	*KRAS p.Q25H* polymorphism associated with development of GBC	Parmanik *et al*[72]
23	GBC (230), controls (230)	Caspase-8 polymorphisms associated with GBC	Srivastava *et al*[73]
24	GBC (51)	p53 mutation are early events in the evolution of GBC	Agrawal *et al*[74]
25	GBC (185), controls (195)	*CYP7A1* haplotype associated with GBC	Srivastava *et al*[75]
26	GBC (230), controls (230)	The role of pre-microRNA variants in GBC uncertain	Srivastava *et al*[76]
27	GBC (62)	Most common alteration in the p53 was frameshift mutation at codon 271	Nigam *et al*[77]
28	GBC (40)	High LOH in *CDH1* associated with pathogenesis of GBC	Priya *et al*[78]
29	GBC (212), controls (219)	Studied the *DNMT3B -579* G > T promoter polymorphism	Srivastava *et al*[79]
30	GBC (233), controls (260)	Angiotensin I-converting enzyme insertion/deletion polymorphism associated with GBC	Srivastava *et al*[80]
31	GBC (126), controls (190)	Role of DNA repair pathways GB carcinogenesis	Srivastava *et al*[81]
32	GBC (171),	Patients with *ABCG8* variant allele are at a higher risk of GBC	Srivastava *et al*[82]

	controls (221)		
33	GBC (185), controls (200)	Complement receptor polymorphism associated with pathogenesis of GBC	Srivastava and Mittal[83]
34	GBC (173), controls (204)	Single nucleotide polymorphisms of DNA repair genes *OGG1* and *XRCC1*; associated with low risk for GBC	Srivastava *et al*[84]
35	GBC (144), controls (210)	Role of *CCR5+/Delta32* polymorphism associated with risk of GBC	Srivastava *et al*[85]
36	GBC (124), controls (166)	*IL-1* gene polymorphisms associated with GBC	Vishnoi *et al*[86]
37	GBC (142), controls (217)	*CYP1A1 C* allele frequency associated with GBC	Pandey *et al*[87]
38	-	*CYP7A1* polymorphism associated with GBC	Srivastava *et al*[88]
39	-	The X (+), D haplotype of *APOB* is associated risk for development of GBC	Pandey *et al*[89]
40	-	NAT2 slow acetylator phenotype associated with risk of GBC	Pandey *et al*[90]
41	GBC (129), controls (208)	*LRPAP1* polymorphism associated with GBC	Pandey *et al*[91]
42	GBC (39)	Mutation in codon 12 of the K-ras oncogene associated with GBC, which indicate role of chronic inflammation in gallbladder carcinogenesis.	Singh *et al*[92]
43	GBC (117), controls (137)	The apoB-XbaI gene polymorphism associated with GBC	Singh *et al*[93]

GBC: Gallbladder cancer; GB: Gallbladder.

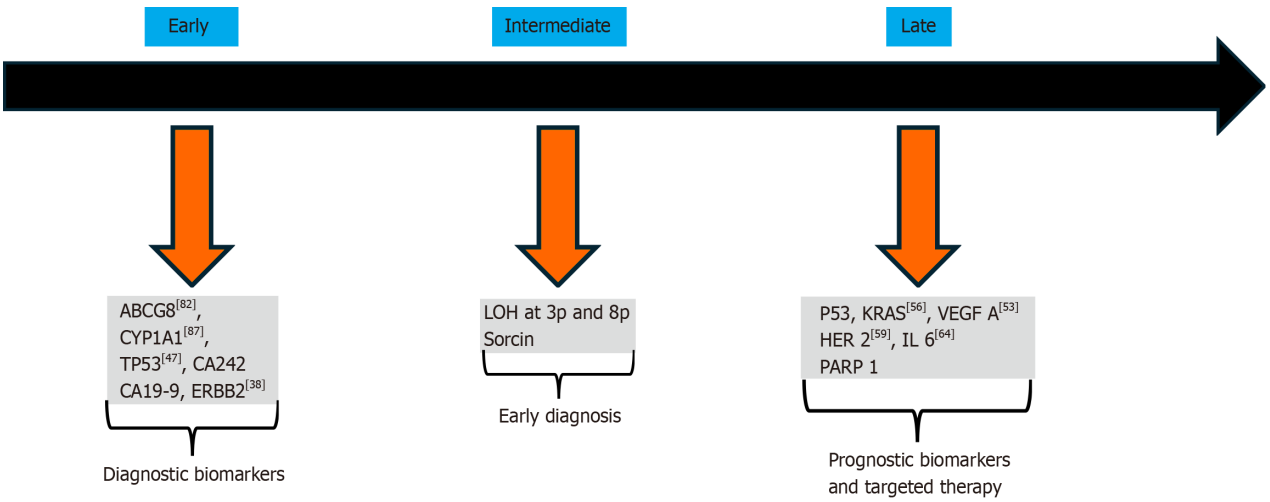


Figure 1 Genes involved in gallbladder cancer pathogenesis at various stages.

(gastric outlet obstruction), and an incidentally detected mass on imaging. In a study conducted by Pandey *et al*[94] the most common symptoms observed were weight loss (reported in 201 patients, 99%) followed by loss of appetite (reported in 197 patients, 97%). Other observed symptoms included pain in the right hypochondrium (reported in 143 patients, 70%), a mass in the right hypochondrium (reported in 107 patients, 53%), jaundice (reported in 79 patients, 39%), and nausea and vomiting (reported in 21 patients, 10%).

Histopathological types

Many patients in India who undergo cholecystectomy do not routinely have their gallbladder specimens sent for histopathology due to financial burden. However, Agarwal *et al*[95] found that patients whose cholecystectomy specimens were sent for histopathological examination (HPE) experienced earlier management if GBC was found in the specimen, achieved a better R0 resection rate, and had longer overall survival (OS) compared to those in whom specimens were not sent. Histologically most of the GBCS are adenocarcinoma whereas most common architectural pattern observed was sheets and acini, with a predominance of columnar cells[96]. Yadav *et al*[97] classified GBC based on fine needle aspiration cytology (FNAC) into various subtypes, including Adenosquamous, mucinous, signet ring, squamous, small cell, mixed adenoneuroendocrine, undifferentiated carcinomas, as well as spindle and giant cell subtypes.

Role of FNAC

Chandra *et al*[98] have introduced a classification system based on FNAC, which includes the following categories: Category 1 (inadequate), Category 2 (negative for malignancy), Category 3 (atypical cells), Category 4 (highly atypical cells suggestive of malignancy), and Category 5 (positive for malignancy). Yadav *et al*[99] reported 28 cases of neuroendocrine tumors (NETs) of the gallbladder. They classified these tumors into three categories based on their differentiation: Well-differentiated (grades 1 and 2), small cell carcinoma (grade 3), and mixed adenoneuroendocrine carcinoma. A positive diagnosis of NET was confirmed by the presence of TTF-1 in the nucleus. Kamboj *et al*[100] published 19 cases of NEC of GB and described the aggressive nature of diseases. Krishnani *et al*[101] reported that FNAC demonstrated a high sensitivity of 90.63% and specificity of 94.74% in detecting carcinoma. For locally advanced or metastatic GBC, preoperative histopathological confirmation is mandatory before initiating chemotherapy. Goyal *et al*[102] concluded that FNAC can be a precise and reliable method for diagnosing GBC in these settings. Shukla *et al*[103] found that the diagnostic accuracy of ultrasonography (USG)-guided FNAC was 95%. This is significantly higher compared to a diagnostic accuracy of 60% on blind aspiration.

Xanthogranulomatous cholecystitis

Xanthogranulomatous cholecystitis (XGC) is malignant masquerade of GBC. Shukla *et al*[104] defined the pathological features of XGC, proposing that they include the presence of foam cells, histiocytes, bile, multinucleate giant cells, and a mixed population of inflammatory cells in varying proportions. These features are observed in a background of pink and granular debris.

Immunohistochemistry

Some immunohistochemistry (IHC) based study also published to diagnosis and prognosticate the disease. Some studies based on IHC have also been published to aid in the diagnosis and prognosis of the disease. Study conducted by Shukla *et al*[105], revealed that although it is a common occurrence in females, GBC does not express hormone receptor. Yadav *et al*[106] suggest that the overexpression of MMP9 and the loss of membranous beta-catenin may be indicative of poor clinical outcomes and advanced disease. Jain *et al*[107] found significant overexpression of KRT7 and SRI in node positive GBC patients compared to node negative GBC patients. This finding may have important implications for the diagnosis and treatment of GBC.

Analysis of cancer-derived extracellular vesicles (EVs) is an emerging method employed to identify potential biomarkers for disease detection and prognosis. Priya *et al*[108] studies GBC cell line- derived EVs and found 16 proteins including haptoglobin which can be served as circulating biomarkers for early detection of GBC. Akhtar *et al*[109] studied specific proteins (MPO, MMP9, and DEFA1) associated with neutrophil degranulation possess signal sequences. They proposed that these proteins could serve as promising circulating markers for early detection of GBC. Priya *et al*[110] studied plasma-derived biomarker that can help in the early detection of GBC. According to their findings, NT5E and ANPEP biomarkers are associated with advanced-stage GBC, while the MME biomarker is linked with early-stage GBC. These studies could be significant in improving the diagnosis and treatment of GBC, allowing for earlier detection and better patient outcomes.

Prognostic markers

Numerous studies have been conducted to identify prognostic markers for GBC. Mishra *et al*[111] found that presence of Higher TNM stage, adjacent organ infiltration, nodal involvement, and jaundice predict poor survival. Negi *et al*[112] found that lymph node (LN) ratio is a strong predictor of outcome after curative resection (CR) for GBC. Shah *et al*[113] found that LN micro metastasis did not correlate with survival. Balachandran *et al*[114] found that Adjuvant therapy, R0 resection and extended cholecystectomy associated with improved survival in patient with GBC. Some other pathological studies are described in Table 3[115-126].

STUDIES ON DIAGNOSTICS AND IMAGING

GBC presents significant diagnostic challenges due to its often-asymptomatic nature in the early stages and nonspecific symptoms as it progresses. Early diagnosis of GBC is crucial for improving patient outcomes. Various imaging modalities are critical for detecting and characterizing gallbladder lesions. USG is frequently chosen as the initial imaging modality for its accessibility and capability to visualize gallbladder abnormalities. Computed tomography (CT) and magnetic resonance imaging (MRI) offer detailed information on tumor extent, invasion of adjacent structures, and the presence of distant metastases. Endoscopic ultrasound (EUS) is a valuable tool for staging GBC due to its high sensitivity in detecting small lesions, assessing local tumor invasion, and facilitating biopsy when necessary. Additionally, positron emission tomography (PET) imaging can help evaluate distant metastases and guide treatment decisions.

Ultrasound is an essential diagnostic tool used for investigating medical conditions in patients. It can detect various abnormalities such as masses, ascites, metastasis, liver infiltration, and involvement of surrounding structures. It is considered as the primary investigation method in most cases. Gallbladder adenocarcinomas can appear as one of three morphologies in USG: Intraluminal mass, diffuse mural thickening, or a mass that replaces the gallbladder. Gallstones are commonly present along with mass in 60%–90% cases. Some retrospective studies were conducted to determine the accuracy of USG in diagnosing GBC. In a study conducted by Pandey *et al*[94], a mass lesion in the gallbladder was found in 87% of the 177 patients examined *via* abdominal sonography. The masses were classified as either intraluminal (59%) or

Table 3 Clinico pathological studies

Serial No.	Sample size	Findings	Ref.
1	GBC (50)	Her2 neu, p53, p16, survivin, COX-2, and EZH-2 expression associated with GBC	Gupta *et al*[115]
2	GBC (200), Dysplasia (32), CC (100)	HER-2/neu overexpression seen in patients with GBC	Jain *et al*[116]
3	GBC (128)	HER 2 and Ki-67 can be used as a prognostic biomarker for gallbladder carcinoma	Halder *et al*[117]
4	-	Combination of ALU247 and cfDNA provides good sensitivity, specificity in diagnosis of GBC	Kumari *et al*[118]
5	-	Proposed a scoring system for XGC	Rajaguru *et al*[119]
6	GBC (34)	Quantitative analysis of cfDNA may aid in early diagnosis	Kumari *et al*[120]
7	GBC (39), cholelithiasis (30), and control (25)	Overexpression of survivin is associated with poor prognosis	Nigam *et al*[121]
8	(GSD, n =30; GBC, n = 39) healthy control (n = 25)	Expression of survivin in peripheral blood could be useful both in the diagnosis and prognosis of GBC	Nigam *et al*[122]
9	GBC (80)	P53 expression is positively correlated with increasing tumor grade, whereas beta-catenin nuclear expression is associated with tumor grade and depth of invasion	Ghosh *et al*[123]
10	9 case of Squamous cell carcinoma	Ultrasound-guided fine-needle aspiration is a useful minimally invasive investigation in the preoperative diagnosis of squamous cell carcinoma of the gallbladder	Gupta and Gupta[124]
11	GBC (55), vontrols (8)	Assay of CA242, CA19-9, CA15-3, and CA125 can be used as marker of carcinoma of the gallbladder	Shukla *et al*[125]
12	GBC (40)	Intraoperative bile cytology can be used for diagnosis of in situ and early invasive GBC	Arora *et al*[126]

GBC: Gallbladder cancer; CC: Chronic cholecystitis.

infiltrative (41%), with irregular margins and higher echogenicity compared to the liver. Infiltrative lesions were more common at the gallbladder neck and fundus. In study by Batra *et al*[127] mass replacing GB was most common findings (73%) on USG followed by presence of gall stone along with mass (54%). Chhabra *et al*[128] demonstrated a new combined type of GBC when GBC present as both thickening and mass replacing GB. Rana *et al*[129] proposed sonographic "Cervix Sign" for GB neck malignancy. The role of USG for screening of GBC is controversial. In a pilot study conducted by Patel *et al*[130] which included 778 patients from high-risk areas, 4 cases of GBC were detected. Anadure *et al*[131] found 6 GBC among 978 high risk healthy participants. Despite showing positive outcomes, it is challenging to conduct screenings for the Indian population due to practical difficulties in real life.

It's quite challenging to differentiate between malignant and benign Thick-walled GB (TWGB). Many studies were conducted in this regard. Gupta *et al*[132] a recommended scoring system called Gallbladder Reporting and Data System can be used to evaluate gallbladder wall features in ultrasound scans. This system considers various factors such as layered appearance, interface with the liver, symmetry and extent of involvement, intramural features like cysts and echogenic foci. By using this system to risk stratify GB lesions; Surgeon can make more informed decisions about treatment options. Gupta *et al*[133] propose an imaging-based algorithm for gallbladder wall thickening. They suggest that diffuse asymmetrical thickening or focal thickening, discontinuous mucosa or breach in mucosa, loss of layered pattern in the gallbladder, high mean systolic velocity in color Doppler, and high shear velocity in Doppler are more indicative of malignant gallbladder wall thickening. Kapoor *et al*[134] proposed that elastography effectively distinguishes between benign and malignant gallbladder wall thickening. Combining this technique with sonography enables early-stage diagnosis of gallbladder carcinoma, highlighting its value as a diagnostic tool. Kalage *et al*[135] suggested a Multiparametric MRI to distinguish between benign thick walls and malignant thick walls. This approach includes Diffusion-weighted, dynamic contrast-enhanced perfusion, intravoxel incoherent motion, and diffusion tensor sequences. The study found that the Multiparametric MRI technique had a 90% sensitivity and 88% specificity for diagnosing Malignant TWGB, whereas conventional Contrast enhanced MRI had 80% sensitivity and 88% specificity.

Recently some authors studied the utility of EUS fine-needle aspiration (FNA) for evaluation of gallbladder mass. Singla *et al*[136] demonstrated that EUS-FNA is a highly sensitive tool for evaluating gallbladder mass lesions associated with obstructive jaundice. However, due to the low negative predictive value of the test, further evaluation is necessary for cases where FNA results are negative.

CT scan

CT is the diagnosis modality of choice for staging the disease. Kalra *et al*[137] discovered that MDCT exhibited a sensitivity of 72.7%, a specificity of 100%, and an accuracy of 85% in assessing the resectability of GBC. To diagnose

hepatic and vascular invasion by the tumor, CT showed a 100% correlation with surgical findings. According to the study conducted by Kumaran *et al*[138] CT scan has an overall accuracy of 93.3% in staging of GBC. Therefore Dual-phase helical CT is a comprehensive method that can be used for preoperative staging of GBC to determine if it is resectable. Soundararajan *et al*[139] proposed CT can be routinely used to determine gastro-intestinal tract involvement on GBC.

Role of PET–CT

GBC are not pet avid tumors. Standard guidelines do not advocate routine pet scan in GBC. In India Many studies were published exploring the utility of PET-CT in GBC. According to a study conducted by Patkar *et al*[140] found that PET-CT can detect metastatic disease in 46.6% of patients that could not be confidently detected using standard cross-sectional imaging. Goel *et al*[141] found that PET-CT altered the management plan in approximately 25% of resectable GBC cases and 30%-35% of locally advanced cases. Shukla *et al*[142] studied role of PET-CT in incidental GBC and found that MDCT had a sensitivity and positive predictive value (PPV) of 42.8% each for determining residual disease, while PET-CT showed a sensitivity of 28.5% and PPV of 20%. In patients diagnosed incidentally with GBC and no metastatic disease, PET-CT and MDCT appear to offer complementary roles in clinical assessment. Goel *et al*[143] found that, the patients with PET-negative pT1b tumors showed no residual disease, in contrast to PET-positive patients (0% *vs* 33%, $P = 0.028$). They proposed that PET-negative pT1b patients could be monitored closely due to the low risk of relapse. Kumar *et al* [144] investigated the efficacy of PET-CT in detecting tumor recurrence in GBC. Their study demonstrated that PET/CT exhibited a high sensitivity (97.6%) and specificity (90%) for detecting tumor recurrence. These findings suggest that PET-CT can be a valuable tool in the detection of tumor recurrence, Residual tumor in incidental GBC and in cases with suspicious of distant metastasis.

Tumor markers

In patients with GBC Sinha *et al*[145]discovered a significant association between serum levels of tumor markers (such as CA19-9, CEA, CA125, and CA242) and GBC. Agrawal *et al*[146] suggested that CA19-9, CA125 and CEA may serve as predictors of resectability in GBC. They found that elevated levels of CA19-9 and CA125 associated with poorer prognosis in affected patients. The role of different imaging modalities in the diagnosis of GBC is illustrated in Figure 2. Some other studies on diagnostics and imaging modality are described in Table 4[147-157].

STUDIES ON SURGICAL APPROACH AND RESECTION

In this section, we have described various landmark studies published in the literature from India regarding the surgical approaches for GBC. Staging laparoscopy is highly accurate in identifying peritoneal deposits and sub centimetric metastases over liver surface and should be considered for all patients of GBC undergoing surgery. Agarwal *et al*[158] found, staging laparoscopy prevented laparotomy in 23% of patients with GBC. They suggested performing routine staging laparoscopy for GBC patients undergoing surgery. Another study by Agrawal *et al*[159] reported that staging laparoscopy prevented a nontherapeutic laparotomy in 43% of patients initially deemed resectable based on pre-operative imaging. Both of these studies underscored the importance of staging laparoscopy and advocated for its mandatory use in GBC.

TWGB

Surgeons around the world do not widely accept laparoscopic cholecystectomy for TWGB due to the risk of malignancy. Srikanth *et al*[160] in their study proposed that laparoscopic cholecystectomy can be performed in patients with diffuse TWGB. However, there is an increased risk of to open cholecystectomy. Kapoor *et al*[161] proposed an approach of anticipatory extended cholecystectomy for TWGB (Luckow Approach).

Role of 16b1 node

After staging laparoscopy, the usual first step is the sampling of interaortocaval (IAC) LNs. GBC involving the 16b1 (IAC) LN is considered to be metastatic. Agarwal *et al*[162] studied the role of routine frozen-section HPE of the 16b1 LN in the management of GBC. They recommended the routine sampling of the 16b1 node during surgical procedures to prevent non-therapeutic radical resection. Their study found that routine 16b1 LN biopsy prevented such resections in 18.6% of patients. When 16b1 nodes tested positive, Agarwal *et al*[162] treated them along with systemic disease, and abandoned surgery when these nodes were found to be positive. Ghosh *et al*[163] from SGPGIMS, Lucknow echoed the same finding, they found that the median survival for IAC node positive group and patients with distant metastasis were same. However, Aggarwal *et al*[164] advocated that certain cases of GBC with IAC node metastasis may be eligible for CR followed by adjuvant therapy. However, their study was limited by a small sample size.

Extent of resection

According to previous studies, only 10% of patients with GBC are deemed resectable. For Tis and T1a lesions, a simple cholecystectomy with negative margins at the cystic duct is typically effective and can achieve cure rates ranging from 85% to 100%. However, gallbladder lesions classified as T1b and higher often come with nodal metastases, necessitating radical resection. This typically involves en bloc hepatic bed resection (which may include removing 2-3 cm of liver wedge or performing a formal segment IVb and V resection) along with regional lymphadenectomy. The surgical goal is R0 resection, aiming to achieve negative cystic duct margins (CDMs). In cases of positive margins, revision of the duct

Table 4 Studies on diagnostic methods and imaging

Serial No.	Sample size	Findings	Ref.
1	-	PET-CT can be used to rule out metastatic disease and for post-therapy surveillance for recurrence in patients of GBC	Bisht *et al*[147]
2	GBC (38)	Potential utility of CT texture-based radiomics analysis in patients with GBC.	Gupta *et al*[148]
3	GBC (141)	Raised levels of serum CA19-9 beyond 20 units/mL should be used for prognostication purposes after EC	Agrawal *et al*[149]
4	GBC (141)	NMR-based methods can be used as a diagnostic modality for GBC	Sharma *et al*[150]
5	GBC (41)	CEA expression may help in diagnosis of GBC	Mondal *et al*[151]
6	GBC (203)	Discontinuous mucosal lining, diffuse wall thickening, intramural nodules, and cholelithiasis may indicate XGC rather than gallbladder carcinoma	Sureka *et al*[152]
7	GBC (74)	Duodenal involvement significantly decreases resectability but does not preclude resection	Kalayarasan *et al*[153]
8	XGC (31)	Mass-forming XGC mimics GBC	Agarwal *et al*[154]
9	GBC (117)	CA 242 is a promising tumor marker for GBC and performs better than CEA and CA19-9.	Rana *et al*[155]
10	GBC (15)	Dynamic MRI with MRCP is a reliable method of showing gall bladder carcinoma.	Kaza *et al*[156]
11	GBC (60)	Color Doppler USG together can improve pickup rate of GBC	Pradhan *et al*[157]

PET: Positron emission tomography; CT: Computed tomography; GBC: Gallbladder cancer; MRI: Magnetic resonance imaging; MRCP: Magnetic resonance cholangiopancreatography.

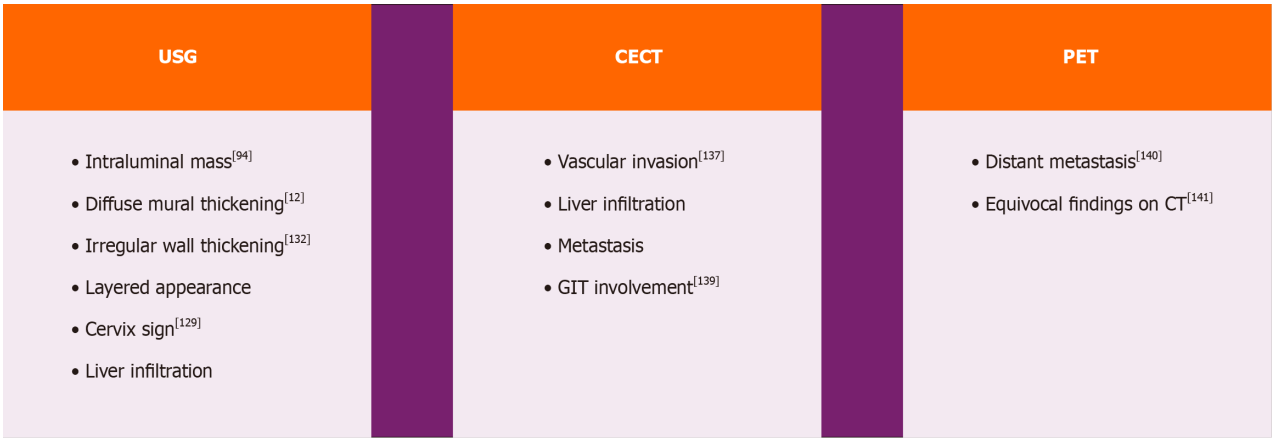


Figure 2 Role of diagnostic modalities in gallbladder cancer. USG: Ultrasonography; CECT: Contrast-enhanced computed tomography; PET: Positron emission tomography.

margin or extrahepatic bile duct (EHBD) excision may be necessary. Studies published in India exploring the ideal surgical approach for GBC have not yet provided concrete recommendations.

Singh *et al*[165] found that CR is the only chance of cure, aggressive surgical approach and improve OS. Wagholikar *et al*[166] advocated that simple cholecystectomy is effective only for GBC limited to the mucosa. However, patients diagnosed with pT1b tumors should undergo extended cholecystectomy. The study proposes that for cases where incidental GBC extends to the muscularis layer, early reoperation to complete an extended cholecystectomy is recommended.

There has been considerable debate regarding the optimal approach to liver resection in GBC, specifically whether anatomical segment IVb and V resection is superior to non-anatomical wedge excision of the liver. There are some studies regarding the same with conflicting results. Pottakkat *et al*[167] demonstrated that the extended criteria for radical resection (Segment 4b and 5) are highly effective, achieving R0 status in over 80% of GBC patients and yielding acceptable long-term outcomes. Nag *et al*[168] from GB Pant Hospital, New Delhi, discovered that there was no significant difference in mean recurrence-free survival (RFS) between segment 4b and 5 resections compared to wedge resection, with 58.2 months *vs* 42.3 months, respectively (P = 0.264). The OS was also similar between both of these groups. Therefore, they concluded that segment 4b and 5 resections were not superior to wedge resection. Tewari *et al*[169] from Banaras Hindu University (BHU) found that wedge resection of the gallbladder achieves adequate oncological clearance in early GBC.

Margin status

Studies have shown that the surgical margin status is the most important factor in determining the overall outcome of liver resection surgeries, rather than the type of resection performed. Behari *et al*[170] found similar results, with patients who underwent R0 resections having significantly better survival rates than those who underwent R1 resections (median 25.8 months *vs* 17.0 months; $P = 0.03$). Hence, the primary objective should be to achieve complete removal of the disease with clear histologic margins.

Frozen section of CDM

Routine use of CDM frozen section analysis is controversial. Some study from India refuted this practice. Jajal *et al*[171] suggest that routine CDM frozen analysis may not be necessary in patients with resectable GBC who do not have jaundice. They found that a positive CDM has comparable survival outcomes to a negative CDM, with similar R0 resection rates and tumor stages. Some authors suggest that routine resection of the common bile duct during surgery may aid in lymphadenectomy and increase LN yield. However, a study by Behari *et al*[170] from India found that EHBD resection does not offer significant survival benefits.

Standard lymphadenectomy

The standard lymphadenectomy for GBC involves removing LNs located along the hepatoduodenal ligament, common hepatic artery, and peri-pancreatic region (stations 8, 12, and 13). Pandey *et al*[172] from BHU proposed this systemic regional lymphadenectomy in GBC gives a good lymph nodal yield and better outcome. Negi *et al*[112] suggested that the retrieval and examination of at least 6 nodes can have a positive impact on the quality of staging and disease-free survival (DFS) in node-negative patients. Goel *et al*[173] from TMH found that for individuals diagnosed with T1b GB cancer, the likelihood of nodal positivity is approximately 21%. Therefore, they recommended that radical surgery, including comprehensive periportal lymphadenectomy, should be considered the standard of care.

Excision of extra-hepatic bile duct

Some authors believe that the presence of obstructive jaundice is a sign of inoperability. Agarwal *et al*[174] conducted a study on 51 patients with GB cancer and obstructive jaundice. Of these 51 patients, 14 underwent resection with curative intent, resulting in a resectability rate of 27.45%. Despite being jaundiced, these patients were able to undergo successful resection. They found a mortality rate of 7.14% and a morbidity rate of 50%. The mean DFS was 23.46 months, with a median of 26 months and a range spanning from 2 to 62 months. Among patients who underwent resection, 50% survived beyond two years. They concluded that Biliary obstruction in GB cancer is not signs of inoperability and resection results in prolongation of survival[174]. Pandey *et al*[172] found that EHBD resection to achieve R0 resection is safe, associated with acceptable postoperative morbidity, and may increase survival. A positive CDM, direct infiltration of the hepatoduodenal ligament, and densely adherent peri-choledochal LNs were the indicators of EHBD resection. K *et al*[175] studied 59 GBC patients who had jaundice. Total of 61.7% and 84%, respectively, of patients underwent CR and non-CR had common bile duct involvement ($P = 0.062$). They found that Patients with GBC and jaundice have better significant survival after CR.

Extended resection in GBC

There are some reserves among surgeons for extended resection in carcinoma GB. As operative techniques improve and new technology develops, there is an increasing trend in extended resection. Commonly performed extended procedures are segmentectomy 4B + 5, extended right hepatectomy, median sectorectomy and hepatopancreaticoduodenectomy. Pottakkat *et al*[167] studied the outcomes of extended resection in GBC and identified postoperative complications in 60% of patients. They achieved acceptable R0 resection (83%) and survival rates. But Behari *et al*[170] could find that only 43% of GBC undergoing extended resection could achieved R0 resection. Singh *et al*[176] from Rajiv Gandhi Cancer institute first to explore PVE followed by extended hepatectomy in GBC. In their study on 14 patients following Neo adjuvant chemo therapy (NACT) and portal vein embolization. Seven (50%) underwent CR (extended hepatectomy). The median OS was 27 months for resectable patients and 15 months for unresectable patients.

Agarwal *et al*'s[177] study, which examined the duodenum's involvement in GBC, revealed that, of the 43 patients with duodenal involvement, 26 had R0 resection (61.9%). Of these, 16 had duodenal sleeve resection (61.54%), 9 had distal gastrectomy with resection of the first part of the duodenum (34.62%), and 1 patient had hepato-pancreatoduodenectomy (HPD; 3.85%). They concluded that duodenal infiltration does not serve as a sign of unresectability or a reason to undergo HPD. For the majority of these patients, a distal gastrectomy combined with resection of the first segment of the duodenum, or a duodenal sleeve resection can accomplish an oncologically appropriate R0 resection[178].

With surgeons now willing for extended resection, further some studies published for resection in presence of metastasis. Patkar *et al*[179] from TMH propose a potential role for aggressive treatment of advanced GBC with limited metastatic burden, such as microscopic disease in the station 16b1 node, low-burden peritoneal disease with deposits smaller than 1 cm in adjacent omentum or diaphragm, isolated N2 disease, or a solitary discontinuous liver metastasis in adjacent liver parenchyma.

Minimally invasive surgery in GBC

With advance laparoscopic and robotic surgery now getting prominence, Agarwal *et al*[180] found that laparoscopic radical cholecystectomy is safe and feasible for selected patients with GBC, and the outcomes are comparable to those of open radical cholecystectomy. Nag *et al*[181] found laparoscopic hepatic bisegmentectomy is safe and feasible. Palanisamy *et al*[182] from GEM hospital published their study and suggested that laparoscopic radical cholecystectomy

may serve as a viable and feasible option for managing GBC, providing effective oncological clearance. Additionally, it offers the typical benefits associated with minimal access procedures. Goel *et al*[183] from TMH suggested robotic radical cholecystectomy is safe and feasible and the short-term results are compared with Open radical cholecystectomy.

Incidentally detected GBC

Incidentally detected carcinoma GB is another debatable topic. Some studies have been published on incidentally detected gallbladder carcinoma from India. Shukla *et al*[184] studied the factors influencing operability in incidentally detected GBC and found that stage is the most important factor in determining resectability. They found that as the T-stage of the disease progressed, the probability of finding residual disease increased, while operability decreased. They also found that incidence of lymph nodal disease is higher for pT1b cancers. Wagholikar *et al*[166] suggested that, incidental GBC extending up to the muscularis requires completion extended cholecystectomy. Although there are no prospective clinical trials, it is widely believed that complete resection of residual disease leads to improved survival. Multiple studies have shown a survival advantage with CR, thereby supporting re-resection in incidental GBC beyond pT1b. Patkar *et al*[185] from TMH, found contrasting results in their study on 425 patients of PT2 of GBC out of which 118 (27.7%) and 307 (72.23%) patients were in the upfront operated GBC and incidental GBC groups, respectively. They found that incidentally detected pT2 GBCs have significantly worse outcomes compared to similarly staged patients undergoing an upfront radical cholecystectomy**.** Some other studies on surgical management are described in Table 5[186-189].

STUDIES ON MULTIMODALITY THERAPY.

Despite improvement in surgical techniques, survival and resection rate of GBC remained the same. Gradually multi-modality therapy evolved with the aim of improving survival. Patkar *et al*[190] published the experience of TMH, Mumbai with largest cohort of 1307 patients with GBC. They advocated peri-operative chemotherapy both in adjuvant and neo adjuvant settings in properly selected patients. We will first discuss adjuvant therapy followed by neoadjuvant therapy and advances made in these fields.

Studies on adjuvant therapy in GBC

The role of adjuvant therapy on increasing survival in GBC is controversial. To date, there have been only a few randomized studies conducted in India exploring the role of adjuvant radiotherapy (RT) or chemo RT (CRT) in resected GBC.

Ostwal *et al*[191] from TMH, Mumbai in their study of 242 resectable stage II and III GBC patients found that patients undergoing R0 resections receiving adjuvant Gemcitabine and cisplatin bases chemotherapy have high completion rates and good tolerance. Kattepur *et al*[192] found that adjuvant chemotherapy reduces distant failure rates but did not improve OS in completely resected GBC patients. They found that lymphovascular invasion important predictor of RFS in T2N0 patients. Some centers tried RT in adjuvant setting. Mahantshetty *et al*[193] from TMH suggested adjuvant RT along with CT improve survival in GBC after resection. Authors used 5 FU bases regimen in their cohort of patients. Choudhary and Asthana[194] studied the effect of adjuvant treatment, including RT, CT, or CRT, following CR and found improved survival compared to surgery alone but the difference was not statistically significant. Agrawal *et al*[195] found that Adjuvant CRT followed by adjuvant chemotherapy improves outcomes in patients with R1 and node-positive disease. There is only one Randomized control trial available that examines the function of CT and RT in adjuvant situations.

The GB-GECCOR trial, a phase II multicenter study, investigated two treatment arms: CAPE-RT (consisting of 2-4 cycles of capecitabine followed by RT: 45 Gy over 25 fractions concurrent with capecitabine: 825 mg/m^2 twice daily, followed by 2-4 additional cycles of capecitabine) *vs* GC (gemcitabine at 1000 mg/m^2 and cisplatin at 25 mg/m^2 administered on days 1 and 8, every 3 wk) following resection. The DFS rate for the GC group was 88.9% *vs* 77.8% for CAPE-RT group. These outcomes support the application of both regimens as appropriate care[196].

Unresectable and metastatic diseases

The appropriate regimen for unresectable and metastatic disease has not yet been defined. Many studies have been published studying different therapies in these settings. Many studies shown that Gemcitabine/cisplatin combination well tolerated and in advanced unresectable GBC[197-199]. Chatni *et al*[200] studied infusion chemotherapy with cisplatin and fluorouracil. Sharma *et al*[201] studied the gemcitabine and oxaliplatin regimen in unresectable GB cancer and found a survival benefit. Same authors studied the efficacy of chemotherapy compared to best supportive care and reported that chemotherapy improved OS and progression free survival (PFS) in unresectable GBC. Ali *et al*[202] in their comparative study between Cisplatin-5-Fluorouracil and Gemcitabine-Cisplatin and found overall more benefit in Gemcitabine-Cisplatin arm. Singh *et al*[203] advocated use of Gemcitabine based regimen in metastatic and advanced GBC which improved PFS.

Currently there is no "standard" second-line therapy after failure of first-line gemcitabine and cisplatin in patients with GBC. Ramaswamy *et al*[204] found that CAP-IRI is a well-tolerated second-line chemotherapeutic regimen in advanced GBC. In GB-SELECT trial they found that single agent irinotecan can be used as second line treatment in palliative setting. Some other important study on Adjuvant therapy in metastatic disease are described in Table 6[205-214].

Table 5 Studies on surgical approaches and resection

Serial No.	Sample size	Findings	Ref.
1	GBC (521)	Surgical resection improves survival in GBC with jaundice	Goel *et al* [186]
2	GBC (97)	Radical cholecystectomy with wedge resection of the liver oncological equivalence compared to formal segment IVb/V excision	Patkar *et al* [187]
3	GBC (20)	The technique of LHBRL is safe and feasible for patients with GBC	Nag *et al* [188]
4	07 incidental GBC	Re-exploration and aggressive resection followed by adjuvant chemotherapy for incidental gallbladder carcinoma are safe and provide hope for long-term survival	Kaman *et al* [189]

GBC: Gallbladder cancer; LHBRL: Laparoscopic hepatic bisegmentectomy with regional lymphadenectomy.

Table 6 Studies on adjuvant therapy on gall bladder carcinoma

Serial No.	Sample size	Findings	Ref.
1	GBC (176)	CT followed by CTRT improves outcomes in patients with limited volume disease	Alam *et al*[205]
2	GBC (550)	CT followed by cCTRT appears to improve survival in responders with good PS	Alam *et al*[206]
3	GBC (38)	Her2neu directed therapy significantly improved survival	Das *et al*[207]
4	GBC (66)	FOLFOX-4 is an effective and well-tolerated regimen as a second-line treatment	Dodagoudar *et al*[208]
5	GBC (87)	CAP-IRI is a well-tolerated second-line chemotherapeutic regimen in advanced GBC	Ramaswamy *et al*[209]
6	GBC (121)	Reduced dose intensity of chemotherapy in GBC	Gangopadhyay *et al*[210]
7	GBC (210)	Use of gem-platinum in Indian patients associated with slightly worse outcomes	Sirohi *et al*[211]
8	-	Autologous immune enhancement therapy associated with, an improvement of the quality of life	Bhamare *et al*[212]
9	GBC (104)	Adjuvant chemoradiation improve survival	Mallick *et al*[213]
10	-	Chemoradiation improve survival in locally advanced GBC	Engineer *et al*[214]

GBC: Gallbladder cancer; CTRT: Chemo-radiotherapy; cCTRT: Consolidation chemoradiation.

STUDIES ON NEOADJUVANT TREATMENT

Surgical resection is the only potential cure for GBC. However, many patients are present with locally advanced state, making it difficult to perform curative surgery. Neoadjuvant therapy can effectively downstage tumors in these patients and help assess disease biology to identify the most suitable candidates for surgery. TMH has taken a step ahead and started using NACT as an option in locally advanced GBC. Chaudhari *et al*[215] introduced the TMH criteria for neoadjuvant chemotherapy in locally advanced or borderline resectable GBC, leading to curative surgical resection in a significant percentage of patients. Agrawal *et al*[216] demonstrated the benefit of neoadjuvant chemo-RT in locally advanced GBC. In their study they have reported Radiologic downstaging of liver involvement is 40.5% and lymphadenopathy is 67.5%[216].

A group of investigators is presently carrying out a prospective clinical experiment called POLCA-GB at TMH in Mumbai. This experiment aims to assess the efficacy of chemotherapy administered alone (four cycles of gemcitabine-cisplatin or gemcitabine-oxaliplatin) *vs* chemotherapy administered in combination with radiation treatment (RT) contemporaneous with gemcitabine, followed by two rounds of gemcitabine-cisplatin or gemcitabine-oxaliplatin chemotherapy. This trial aims to enable potentially CR by downstaging locally advanced GBC. The trial is now in the recruiting stage[217]. Few other series from India have demonstrated a benefit of gemcitabine-platinum based neoadjuvant therapy in GBC described in Table 7[218-221].

CONCLUSION

This review has found significant work and efforts made by India in addressing GBC over the past two decades. India has produced a substantial number of quality research publications on GBC-epidemiology, etiopathogenesis, pathology, surgery, and multimodal treatment approaches. Country has progressed well on surgical management and multimodal

Table 7 Studies on neo-adjuvant therapy on gall bladder carcinoma

Serial No.	Sample size	Findings	Ref.
1	GBC (510)	Surgery and peri-operative systemic therapy associated with improved survival	Patkar *et al*[218]
2	GBC (28)	Locally advanced GBC may benefit from neoadjuvant chemoradiation	Engineer *et al*[219]
3	GBC (37)	Neoadjuvant chemotherapy in patients with locally advanced gallbladder cancer	Sirohi *et al*[220]
4	GBC (21)	Resection after neoadjuvant chemotherapy improve survival	Selvakumar *et al*[221]

GBC: Gallbladder cancer.

treatment strategies. However, there remains a lack of specific research on etiopathogenesis, early diagnosis, preventive measures, and emerging treatments such as immunotherapy. The coming decades should prioritize efforts towards screening strategy in high-risk zone, early detection, and the development of well-defined treatment protocol/ policy. Collaborative international research would be useful to achieve and overcome the deficient areas.

FOOTNOTES

Author contributions: Kumar A designed the concept, revised and edited the manuscript; Sarangi Y and Gupta A jointly wrote the manuscript; Sharma A helped in literature search.

Conflict-of-interest statement: Dr. Kumar has nothing to disclose.

Country of origin: India

ORCID number: Ashok Kumar 0000-0003-3959-075X; Yajnadatta Sarangi 0000-0003-4951-6705; Annapurna Gupta 0009-0000-7603-6788; Aarti Sharma 0000-0002-8744-1268.

S-Editor: Lin C
L-Editor: A
P-Editor: Zhao YQ

REFERENCES

1 **Zhu AX**, Hong TS, Hezel AF, Kooby DA. Current management of gallbladder carcinoma. *Oncologist* 2010; **15**: 168-181 [PMID: 20147507 DOI: 10.1634/theoncologist.2009-0302]
2 **Bray F**, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I, Jemal A. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2024; **74**: 229-263 [PMID: 38572751 DOI: 10.3322/caac.21834]
3 **Dutta U**, Bush N, Kalsi D, Popli P, Kapoor VK. Epidemiology of gallbladder cancer in India. *Chin Clin Oncol* 2019; **8**: 33 [PMID: 31484488 DOI: 10.21037/cco.2019.08.03]
4 **Phadke PR**, Mhatre SS, Budukh AM, Dikshit RP. Trends in gallbladder cancer incidence in the high- and low-risk regions of India. *Indian J Med Paediatr Oncol* 2019; **40**: 90-93 [DOI: 10.4103/ijmpo.ijmpo_164_18]
5 **S ST**, Krishnan SK, Das P, Sudarshan KL, Kotian CM, Santhappan S, Vishwakarma MB, N S, Mathur P. Descriptive Epidemiology of Gastrointestinal Cancers: Results from National Cancer Registry Programme, India. *Asian Pac J Cancer Prev* 2022; **23**: 409-418 [PMID: 35225451 DOI: 10.31557/APJCP.2022.23.2.409]
6 **Mhatre SS**, Nagrani RT, Budukh A, Chiplunkar S, Badwe R, Patil P, Laversanne M, Rajaraman P, Bray F, Dikshit R. Place of birth and risk of gallbladder cancer in India. *Indian J Cancer* 2016; **53**: 304-308 [PMID: 28071634 DOI: 10.4103/0019-509X.197723]
7 **Gupta SK**, Ansari MA, Shukla VK. What makes the Gangetic belt a fertile ground for gallbladder cancers? *J Surg Oncol* 2005; **91**: 143-144 [PMID: 16028289 DOI: 10.1002/jso.20292]
8 **Mishra RR**, Tewari M, Shukla HS. Helicobacter pylori and pathogenesis of gallbladder cancer. *J Gastroenterol Hepatol* 2011; **26**: 260-266 [PMID: 21261714 DOI: 10.1111/j.1440-1746.2010.06435.x]
9 **Nath G**, Singh YK, Kumar K, Gulati AK, Shukla VK, Khanna AK, Tripathi SK, Jain AK, Kumar M, Singh TB. Association of carcinoma of the gallbladder with typhoid carriage in a typhoid endemic area using nested PCR. *J Infect Dev Ctries* 2008; **2**: 302-307 [PMID: 19741293 DOI: 10.3855/jidc.226]
10 **Tewari M**, Mishra RR, Shukla HS. Salmonella typhi and gallbladder cancer: report from an endemic region. *Hepatobiliary Pancreat Dis Int*

2010; **9**: 524-530 [PMID: 20943463]

11 **Mhatre S**, Lacey B, Sherliker P, Chatterjee N, Rajaraman P, Goel M, Patkar S, Ostwal V, Patil P, Shrikhande SV, Chitkara G, Badwe R, Lewington S, Dikshit R. Reproductive factors and gall-bladder cancer, and the effect of common genetic variants on these associations: a case-control study in India. *Int J Epidemiol* 2022; **51**: 789-798 [PMID: 34550362 DOI: 10.1093/ije/dyab197]

12 **Mhatre S**, Rajaraman P, Chatterjee N, Bray F, Goel M, Patkar S, Ostwal V, Patil P, Manjrekar A, Shrikhande SV, Badwe R, Dikshit R. Mustard oil consumption, cooking method, diet and gallbladder cancer risk in high- and low-risk regions of India. *Int J Cancer* 2020; **147**: 1621-1628 [PMID: 32142159 DOI: 10.1002/ijc.32952]

13 **Mishra K**, Behari A, Shukla P, Tsuchiya Y, Endoh K, Asai T, Ikoma T, Nakamura K, Kapoor VK. Risk factors for gallbladder cancer development in northern India: A gallstones-matched, case-control study. *Indian J Med Res* 2021; **154**: 699-706 [PMID: 35532588 DOI: 10.4103/ijmr.IJMR_201_19]

14 **Zatonski WA**, Lowenfels AB, Boyle P, Maisonneuve P, Bueno de Mesquita HB, Ghadirian P, Jain M, Przewozniak K, Baghurst P, Moerman CJ, Simard A, Howe GR, McMichael AJ, Hsieh CC, Walker AM. Epidemiologic aspects of gallbladder cancer: a case-control study of the SEARCH Program of the International Agency for Research on Cancer. *J Natl Cancer Inst* 1997; **89**: 1132-1138 [PMID: 9262251 DOI: 10.1093/jnci/89.15.1132]

15 **Mhatre S**, Richmond RC, Chatterjee N, Rajaraman P, Wang Z, Zhang H, Badwe R, Goel M, Patkar S, Shrikhande SV, Patil PS, Davey Smith G, Relton CL, Dikshit RP. The Role of Gallstones in Gallbladder Cancer in India: A Mendelian Randomization Study. *Cancer Epidemiol Biomarkers Prev* 2021; **30**: 396-403 [PMID: 33187967 DOI: 10.1158/1055-9965.EPI-20-0919]

16 **Dutta U**, Nagi B, Garg PK, Sinha SK, Singh K, Tandon RK. Patients with gallstones develop gallbladder cancer at an earlier age. *Eur J Cancer Prev* 2005; **14**: 381-385 [PMID: 16030429 DOI: 10.1097/00008469-200508000-00011]

17 **Narang S**, Goyal P, Bal M, Bandlish U, Goyal S. Gall stones size, number, biochemical analysis and lipidogram- an association with gall bladder cancer: a study of 200 cases. *Int J Cancer Ther Oncol* 2014; **2**: 020310 [DOI: 10.14319/ijcto.0203.10]

18 **Singh A**, Singh G, Kaur K, Goyal G, Saini G, Sharma D. Histopathological Changes in Gallbladder Mucosa Associated with Cholelithiasis: A Prospective Study. *Niger J Surg* 2019; 25: 21-25 [PMID: 31007507 DOI: 10.4103/njs.NJS_15_18]

19 **Sharma N**, Yadav M, Tripathi G, Mathew B, Bindal V, Falari S, Pamecha V, Maras JS. Bile multi-omics analysis classifies lipid species and microbial peptides predictive of carcinoma of gallbladder. *Hepatology* 2022; **76**: 920-935 [PMID: 35357716 DOI: 10.1002/hep.32496]

20 **Shridhar K**, Krishnatreya M, Kumar R, Kondal D, Bhattacharyya M, Kalita B, Snehil P, Singh AK, Kataki AC, Ghosh A, D Prabhakaran, Prabhakaran P, Dhillon PK. Household cooking fuel and gallbladder cancer risk: a multi-centre case-control study in India. *Cancer Causes Control* 2024; **35**: 281-292 [PMID: 37733135 DOI: 10.1007/s10552-023-01787-8]

21 **Jain K**, Sreenivas V, Velpandian T, Kapil U, Garg PK. Risk factors for gallbladder cancer: a case-control study. *Int J Cancer* 2013; **132**: 1660-1666 [PMID: 22890893 DOI: 10.1002/ijc.27777]

22 **Bhattacharjee PK**, Nanda D. Prospective observational study on cholelithiasis in patients with carcinoma gall bladder in a tertiary referral hospital of Eastern India. *J Cancer Res Ther* 2019; **15**: 153-156 [PMID: 30880772 DOI: 10.4103/jcrt.JCRT_939_17]

23 **Madhawi R**, Pandey A, Raj S, Mandal M, Devi S, Sinha PK, Singh RK. Geographical pattern of carcinoma gallbladder in Bihar and its association with river Ganges and arsenic levels: Retrospective individual consecutive patient data from Regional Cancer Centre. *South Asian J Cancer* 2018; **7**: 167-170 [PMID: 30112331 DOI: 10.4103/sajc.sajc_37_18]

24 **Tyagi BB**, Manoharan N, Raina V. Risk factors for gallbladder cancer : A population based case-control study in Delhi. *Indian J Med Paediatr Oncol* 2008; **29**: 16-26 [DOI: 10.4103/0971-5851.51442]

25 **Khan I**, Panda N, Banerjee M, Das R. Epidemiological factors in gall bladder cancer in eastern India-a single centre study. *Indian J Surg Oncol* 2013; **4**: 67-72 [PMID: 24426702 DOI: 10.1007/s13193-012-0203-x]

26 **Panda D**, Sharma A, Shukla NK, Jaiswal R, Dwivedi S, Raina V, Mohanti BK, Deo SV, Patra S. Gall bladder cancer and the role of dietary and lifestyle factors: a case-control study in a North Indian population. *Eur J Cancer Prev* 2013; **22**: 431-437 [PMID: 23462456 DOI: 10.1097/CEJ.0b013e32835f3b45]

27 **Bansal VK**, Misra MC, Chaubal G, Datta Gupta S, Das B, Ahuja V, Sagar S. Helicobacter pylori in gallbladder mucosa in patients with gallbladder disease. *Indian J Gastroenterol* 2012; **31**: 57-60 [PMID: 22350820 DOI: 10.1007/s12664-012-0162-8]

28 **Mathur SK**, Duhan A, Singh S, Aggarwal M, Aggarwal G, Sen R, Garg S. Correlation of gallstone characteristics with mucosal changes in gall bladder. *Trop Gastroenterol* 2012; **33**: 39-44 [PMID: 22803294 DOI: 10.7869/tg.2012.6]

29 **Srivastava M**, Sharma A, Kapoor VK, Nagana Gowda GA. Stones from cancerous and benign gallbladders are different: A proton nuclear magnetic resonance spectroscopy study. *Hepatol Res* 2008; **38**: 997-1005 [PMID: 18507688 DOI: 10.1111/j.1872-034X.2008.00356.x]

30 **Sharma V**, Chauhan VS, Nath G, Kumar A, Shukla VK. Role of bile bacteria in gallbladder carcinoma. *Hepatogastroenterology* 2007; **54**: 1622-1625 [PMID: 18019679]

31 **Misra V**, Misra SP, Dwivedi M, Shouche Y, Dharne M, Singh PA. Helicobacter pylori in areas of gastric metaplasia in the gallbladder and isolation of H. pylori DNA from gallstones. *Pathology* 2007; **39**: 419-424 [PMID: 17676484 DOI: 10.1080/00313020701444473]

32 **Kumar JR**, Tewari M, Rai A, Sinha R, Mohapatra SC, Shukla HS. An objective assessment of demography of gallbladder cancer. *J Surg Oncol* 2006; **93**: 610-614 [PMID: 16724352 DOI: 10.1002/jso.20526]

33 **Vaishnavi C**, Kochhar R, Singh G, Kumar S, Singh S, Singh K. Epidemiology of typhoid carriers among blood donors and patients with biliary, gastrointestinal and other related diseases. *Microbiol Immunol* 2005; **49**: 107-112 [PMID: 15722595 DOI: 10.1111/j.1348-0421.2005.tb03709.x]

34 **Shukla VK**, Prakash A, Chauhan VS, Singh S, Puneet. Biliary nitrate and risk of carcinoma of the gallbladder. *Eur J Cancer Prev* 2004; **13**: 355-356 [PMID: 15554566 DOI: 10.1097/01.cej.0000137514.48974.89]

35 **Shukla VK**, Adukia TK, Singh SP, Mishra CP, Mishra RN. Micronutrients, antioxidants, and carcinoma of the gallbladder. *J Surg Oncol* 2003; **84**: 31-35 [PMID: 12949988 DOI: 10.1002/jso.10283]

36 **Shukla VK**, Rastogi AN, Adukia TK, Raizada RB, Reddy DC, Singh S. Organochlorine pesticides in carcinoma of the gallbladder: a case-control study. *Eur J Cancer Prev* 2001; **10**: 153-156 [PMID: 11330456 DOI: 10.1097/00008469-200104000-00006]

37 **Gupta SC**, Misra V, Singh PA, Roy A, Misra SP, Gupta AK. Gall stones and carcinoma gall bladder. *Indian J Pathol Microbiol* 2000; **43**: 147-154 [PMID: 11217272]

38 **Iyer P**, Shrikhande SV, Ranjan M, Joshi A, Gardi N, Prasad R, Dharavath B, Thorat R, Salunkhe S, Sahoo B, Chandrani P, Kore H, Mohanty B, Chaudhari V, Choughule A, Kawle D, Chaudhari P, Ingle A, Banavali S, Gera P, Ramadwar MR, Prabhash K, Barreto SG, Dutt S, Dutt A. ERBB2 and KRAS alterations mediate response to EGFR inhibitors in early stage gallbladder cancer. *Int J Cancer* 2019; **144**: 2008-2019

[PMID: 30304546 DOI: 10.1002/ijc.31916]

39 **Kazmi HR**, Chandra A, Nigam J, Noushif M, Parmar D, Gupta V. Prognostic significance of K-ras codon 12 mutation in patients with resected gallbladder cancer. *Dig Surg* 2013; **30**: 233-239 [PMID: 23838952 DOI: 10.1159/000353133]

40 **Gupta V**, Goel MM, Chandra A, Gupta P, Kumar S, Nigam J. Expression and clinicopathological significance of antiapoptotis protein survivin in gallbladder cancer. *Indian J Pathol Microbiol* 2016; **59**: 143-147 [PMID: 27166029 DOI: 10.4103/0377-4929.182035]

41 **Kumari N**, Kapoor VK, Krishnani N, Kumar K, Baitha DK. Role of C-erbB2 expression in gallbladder cancer. *Indian J Pathol Microbiol* 2012; **55**: 75-79 [PMID: 22499306 DOI: 10.4103/0377-4929.94862]

42 **Misra S**, Chaturvedi A, Goel MM, Mehrotra R, Sharma ID, Srivastava AN, Misra NC. Overexpression of p53 protein in gallbladder carcinoma in North India. *Eur J Surg Oncol* 2000; **26**: 164-167 [PMID: 10744937 DOI: 10.1053/ejso.1999.0763]

43 **Singh TD**, Gupta S, Shrivastav BR, Tiwari PK. Epigenetic profiling of gallbladder cancer and gall stone diseases: Evaluation of role of tumour associated genes. *Gene* 2016; **576**: 743-752 [PMID: 26456195 DOI: 10.1016/j.gene.2015.10.004]

44 **Tekcham DS**, Gupta S, Shrivastav BR, Tiwari PK. Epigenetic Downregulation of PTEN in Gallbladder Cancer. *J Gastrointest Cancer* 2017; **48**: 110-116 [PMID: 28124240 DOI: 10.1007/s12029-017-9919-8]

45 **Rai R**, Tewari M, Kumar M, Singh TB, Shukla HS. Expression profile of cholecystokinin type-A receptor in gallbladder cancer and gallstone disease. *Hepatobiliary Pancreat Dis Int* 2011; **10**: 408-414 [PMID: 21813391 DOI: 10.1016/S1499-3872(11)60069-6]

46 **Yadav S**, DE Sarkar N, Kumari N, Krishnani N, Kumar A, Mittal B. Targeted Gene Sequencing of Gallbladder Carcinoma Identifies High-impact Somatic and Rare Germline Mutations. *Cancer Genomics Proteomics* 2017; **14**: 495-506 [PMID: 29109099 DOI: 10.21873/cgp.20059]

47 **Kumari N**, Corless CL, Warrick A, Beadling C, Nelson D, Neff T, Krishnani N, Kapoor VK. Mutation profiling in gallbladder cancer in Indian population. *Indian J Pathol Microbiol* 2014; **57**: 9-12 [PMID: 24739824 DOI: 10.4103/0377-4929.130849]

48 **Priya TP**, Kapoor VK, Krishnani N, Agrawal V, Agarwal S. Fragile histidine triad (FHIT) gene and its association with p53 protein expression in the progression of gall bladder cancer. *Cancer Invest* 2009; **27**: 764-773 [PMID: 19452299 DOI: 10.1080/07357900802711304]

49 **Jain K**, Mohapatra T, Das P, Misra MC, Gupta SD, Ghosh M, Kabra M, Bansal VK, Kumar S, Sreenivas V, Garg PK. Sequential occurrence of preneoplastic lesions and accumulation of loss of heterozygosity in patients with gallbladder stones suggest causal association with gallbladder cancer. *Ann Surg* 2014; **260**: 1073-1080 [PMID: 24827397 DOI: 10.1097/SLA.0000000000000495]

50 **Pandey SN**, Jain M, Nigam P, Choudhuri G, Mittal B. Genetic polymorphisms in GSTM1, GSTT1, GSTP1, GSTM3 and the susceptibility to gallbladder cancer in North India. *Biomarkers* 2006; **11**: 250-261 [PMID: 16760134 DOI: 10.1080/13547500600648697]

51 **Saxena R**, Chakrapani B, Sarath Krishnan MP, Gupta A, Gupta S, Das J, Gupta SC, Mirza AA, Rao S, Goyal B. Next generation sequencing uncovers multiple miRNAs associated molecular targets in gallbladder cancer patients. *Sci Rep* 2023; **13**: 19101 [PMID: 37925508 DOI: 10.1038/s41598-023-44767-3]

52 **Anjali K**, Singh D, Kumar P, Kumar T, Narayan G, Singh S. PARP1 rs1136410 (A/G) polymorphism is associated with early age of onset of gallbladder cancer. *Eur J Cancer Prev* 2022; **31**: 311-317 [PMID: 34406176 DOI: 10.1097/CEJ.0000000000000708]

53 **Singh P**, Jain SL, Sakhuja P, Agarwal A. Expression of VEGF-A, HER2/neu, and KRAS in gall bladder carcinoma and their correlation with clinico-pathological parameters. *Indian J Pathol Microbiol* 2021; **64**: 687-692 [PMID: 34673587 DOI: 10.4103/IJPM.IJPM_248_20]

54 **Singh N**, Kazim SN, Sultana R, Tiwari D, Borkotoky R, Kakati S, Nath Das N, Kumar Saikia A, Bose S. Oxidative stress and deregulations in base excision repair pathway as contributors to gallbladder anomalies and carcinoma - a study involving North-East Indian population. *Free Radic Res* 2019; **53**: 473-485 [PMID: 31117842 DOI: 10.1080/10715762.2019.1606423]

55 **Shukla SK**, Singh G, Shahi KS, Bhuvan, Pant P. Genetic Changes of P(53) and Kras in Gallbladder Carcinoma in Kumaon Region of Uttarakhand. *J Gastrointest Cancer* 2020; **51**: 552-559 [PMID: 31396884 DOI: 10.1007/s12029-019-00283-0]

56 **Shabnam B**, Padmavathi G, Banik K, Girisa S, Monisha J, Sethi G, Fan L, Wang L, Mao X, Kunnumakkara AB. Sorcin a Potential Molecular Target for Cancer Therapy. *Transl Oncol* 2018; **11**: 1379-1389 [PMID: 30216763 DOI: 10.1016/j.tranon.2018.08.015]

57 **Yadav S**, Chandra A, Kumar A, Mittal B. Association of TERT-CLPTM1L and 8q24 Common Genetic Variants with Gallbladder Cancer Susceptibility and Prognosis in North Indian Population. *Biochem Genet* 2018; **56**: 267-282 [PMID: 29450669 DOI: 10.1007/s10528-018-9843-z]

58 **Dixit R**, Pandey M, Tripathi SK, Dwivedi AN, Shukla VK. Comparative Analysis of Mutational Profile of Sonic hedgehog Gene in Gallbladder Cancer. *Dig Dis Sci* 2017; **62**: 708-714 [PMID: 28058596 DOI: 10.1007/s10620-016-4438-1]

59 **Pujani M**, Makker I, Makker A, Jetley S, Goel MM. Expression of Human Epidermal Growth Factor Receptor (Her 2/neu) and Proliferative Marker Ki-67: Association with Clinicopathological Parameters in Gallbladder Carcinoma. *Asian Pac J Cancer Prev* 2016; **17**: 3903-3909 [PMID: 27644637]

60 **Kazmi HR**, Chandra A, Kumar S, Satyam LK, Gupta A, Nigam J, Srivastava M, Mittal B. A let-7 microRNA binding site polymorphism in the KRAS 3'UTR is associated with increased risk and reduced survival for gallbladder cancer in North Indian population. *J Cancer Res Clin Oncol* 2016; **142**: 2577-2583 [PMID: 27620744 DOI: 10.1007/s00432-016-2254-9]

61 **Tekcham DS**, Poojary SS, Bhunia S, Barbhuiya MA, Gupta S, Shrivastav BR, Tiwari PK. Epigenetic regulation of APC in the molecular pathogenesis of gallbladder cancer. *Indian J Med Res* 2016; **143**: S82-S90 [PMID: 27748282 DOI: 10.4103/0971-5916.191792]

62 **Sharma P**, Bhunia S, Poojary SS, Tekcham DS, Barbhuiya MA, Gupta S, Shrivastav BR, Tiwari PK. Global methylation profiling to identify epigenetic signature of gallbladder cancer and gallstone disease. *Tumour Biol* 2016; **37**: 14687-14699 [PMID: 27623942 DOI: 10.1007/s13277-016-5355-9]

63 **Kumar N**, Khan MA, Kumar N; Rigvardhan, Ranjan R, Hazra N. Epidermal growth factor receptor expression in carcinoma gallbladder: A prospective study in Indian scenario. *J Cancer Res Ther* 2016; **12**: 959-962 [PMID: 27461681 DOI: 10.4103/0973-1482.179063]

64 **Patil RS**, Shah SU, Shrikhande SV, Goel M, Dikshit RP, Chiplunkar SV. IL17 producing γδT cells induce angiogenesis and are associated with poor survival in gallbladder cancer patients. *Int J Cancer* 2016; **139**: 869-881 [PMID: 27062572 DOI: 10.1002/ijc.30134]

65 **Dixit R**, Singh G, Pandey M, Basu S, Bhartiya SK, Singh KK, Shukla VK. Association of Methylenetetrahydrafolate Reductase Gene Polymorphism (MTHFR) in Patients with Gallbladder Cancer. *J Gastrointest Cancer* 2016; **47**: 55-60 [PMID: 26687138 DOI: 10.1007/s12029-015-9794-0]

66 **Poojary SS**, Mishra G, Gupta S, Shrivastav BR, Tiwari PK. Dysfunction of subtelomeric methylation and telomere length in gallstone disease and gallbladder cancer patients of North Central India. *J Hepatobiliary Pancreat Sci* 2016; **23**: 276-282 [PMID: 26856965 DOI: 10.1002/jhbp.332]

67 **Dwivedi S**, Agrawal S, Singh S, Madeshiya AK, Singh D, Mahdi AA, Chandra A. Association of Cytochrome-17 (MspA1) Gene Polymorphism with Risk of Gall Bladder Stones and Cancer in North India. *Asian Pac J Cancer Prev* 2015; **16**: 5557-5563 [PMID: 26225710

DOI: 10.7314/APJCP.2015.16.13.5557]
68 **Sharma KL**, Misra S, Kumar A, Mittal B. Association of liver X receptors (LXRs) genetic variants to gallbladder cancer susceptibility. *Tumour Biol* 2013; **34**: 3959-3966 [PMID: 23838803 DOI: 10.1007/s13277-013-0984-8]
69 **Mishra K**, Behari A, Kapoor VK, Khan MS, Prakash S, Agrawal S. Vascular endothelial growth factor single-nucleotide polymorphism in gallbladder cancer. *J Gastroenterol Hepatol* 2013; **28**: 1678-1685 [PMID: 23962084 DOI: 10.1111/jgh.12343]
70 **Maurya SK**, Tewari M, Shukla HS. Gallbladder carcinoma: high rate of mitochondrial D-loop mutations. *Diagn Mol Pathol* 2013; **22**: 119-122 [PMID: 23628824 DOI: 10.1097/PDM.0b013e31827a0d5a]
71 **Srivastava A**, Sharma KL, Srivastava N, Misra S, Mittal B. Significant role of estrogen and progesterone receptor sequence variants in gallbladder cancer predisposition: a multi-analytical strategy. *PLoS One* 2012; **7**: e40162 [PMID: 22808109 DOI: 10.1371/journal.pone.0040162]
72 **Pramanik V**, Sarkar BN, Kar M, Das G, Malay BK, Sufia KK, Lakkakula BV, Vadlamudi RR. A novel polymorphism in codon 25 of the KRAS gene associated with gallbladder carcinoma patients of the eastern part of India. *Genet Test Mol Biomarkers* 2011; **15**: 431-434 [PMID: 21375404 DOI: 10.1089/gtmb.2010.0194]
73 **Srivastava K**, Srivastava A, Mittal B. Caspase-8 polymorphisms and risk of gallbladder cancer in a northern Indian population. *Mol Carcinog* 2010; **49**: 684-692 [PMID: 20564345 DOI: 10.1002/mc.20641]
74 **Agrawal V**, Goel A, Krishnani N, Pandey R, Agrawal S, Kapoor VK. p53, carcinoembryonic antigen and carbohydrate antigen 19.9 expression in gall bladder cancer, precursor epithelial lesions and xanthogranulomatous cholecystitis. *J Postgrad Med* 2010; **56**: 262-266 [PMID: 20935395 DOI: 10.4103/0022-3859.70933]
75 **Srivastava A**, Choudhuri G, Mittal B. CYP7A1 (-204 A>C; rs3808607 and -469 T>C; rs3824260) promoter polymorphisms and risk of gallbladder cancer in North Indian population. *Metabolism* 2010; **59**: 767-773 [PMID: 20005541 DOI: 10.1016/j.metabol.2009.09.021]
76 **Srivastava K**, Srivastava A, Mittal B. Common genetic variants in pre-microRNAs and risk of gallbladder cancer in North Indian population. *J Hum Genet* 2010; **55**: 495-499 [PMID: 20520619 DOI: 10.1038/jhg.2010.54]
77 **Nigam P**, Misra U, Negi TS, Mittal B, Choudhuri G. Alterations of p53 gene in gallbladder cancer patients of North India. *Trop Gastroenterol* 2010; **31**: 96-100 [PMID: 20862982]
78 **Priya TP**, Kapoor VK, Krishnani N, Agrawal V, Agrawal S. Role of E-cadherin gene in gall bladder cancer and its precursor lesions. *Virchows Arch* 2010; **456**: 507-514 [PMID: 20376482 DOI: 10.1007/s00428-010-0908-6]
79 **Srivastava K**, Srivastava A, Mittal B. DNMT3B -579 G>T promoter polymorphism and risk of gallbladder carcinoma in North Indian population. *J Gastrointest Cancer* 2010; **41**: 248-253 [PMID: 20480259 DOI: 10.1007/s12029-010-9156-x]
80 **Srivastava K**, Srivastava A, Mittal B. Angiotensin I-converting enzyme insertion/deletion polymorphism and increased risk of gall bladder cancer in women. *DNA Cell Biol* 2010; **29**: 417-422 [PMID: 20438364 DOI: 10.1089/dna.2010.1033]
81 **Srivastava K**, Srivastava A, Mittal B. Polymorphisms in ERCC2, MSH2, and OGG1 DNA repair genes and gallbladder cancer risk in a population of Northern India. *Cancer* 2010; **116**: 3160-3169 [PMID: 20564624 DOI: 10.1002/cncr.25063]
82 **Srivastava A**, Tulsyan S, Pandey SN, Choudhuri G, Mittal B. Single nucleotide polymorphism in the ABCG8 transporter gene is associated with gallbladder cancer susceptibility. *Liver Int* 2009; **29**: 831-837 [PMID: 19018975 DOI: 10.1111/j.1478-3231.2008.01907.x]
83 **Srivastava A**, Mittal B. Complement receptor 1 (A3650G RsaI and intron 27 HindIII) polymorphisms and risk of gallbladder cancer in north Indian population. *Scand J Immunol* 2009; **70**: 614-620 [PMID: 19906204 DOI: 10.1111/j.1365-3083.2009.02329.x]
84 **Srivastava A**, Srivastava K, Pandey SN, Choudhuri G, Mittal B. Single-nucleotide polymorphisms of DNA repair genes OGG1 and XRCC1: association with gallbladder cancer in North Indian population. *Ann Surg Oncol* 2009; **16**: 1695-1703 [PMID: 19266243 DOI: 10.1245/s10434-009-0354-3]
85 **Srivastava A**, Pandey SN, Choudhuri G, Mittal B. CCR5 Delta32 polymorphism: associated with gallbladder cancer susceptibility. *Scand J Immunol* 2008; **67**: 516-522 [PMID: 18405329 DOI: 10.1111/j.1365-3083.2008.02097.x]
86 **Vishnoi M**, Pandey SN, Choudhuri G, Mittal B. IL-1 gene polymorphisms and genetic susceptibility of gallbladder cancer in a north Indian population. *Cancer Genet Cytogenet* 2008; **186**: 63-68 [PMID: 18940468 DOI: 10.1016/j.cancergencyto.2008.05.004]
87 **Pandey SN**, Choudhuri G, Mittal B. Association of CYP1A1 Msp1 polymorphism with tobacco-related risk of gallbladder cancer in a north Indian population. *Eur J Cancer Prev* 2008; **17**: 77-81 [PMID: 18287863 DOI: 10.1097/CEJ.0b013e3282b6fdd2]
88 **Srivastava A**, Pandey SN, Choudhuri G, Mittal B. Role of genetic variant A-204C of cholesterol 7alpha-hydroxylase (CYP7A1) in susceptibility to gallbladder cancer. *Mol Genet Metab* 2008; **94**: 83-89 [PMID: 18178499 DOI: 10.1016/j.ymgme.2007.11.014]
89 **Pandey SN**, Srivastava A, Dixit M, Choudhuri G, Mittal B. Haplotype analysis of signal peptide (insertion/deletion) and XbaI polymorphisms of the APOB gene in gallbladder cancer. *Liver Int* 2007; **27**: 1008-1015 [PMID: 17696941 DOI: 10.1111/j.1478-3231.2007.01516.x]
90 **Pandey SN**, Modi DR, Choudhuri G, Mittall B. Slow acetylator genotype of N-acetyl transferase2 (NAT2) is associated with increased susceptibility to gallbladder cancer: the cancer risk not modulated by gallstone disease. *Cancer Biol Ther* 2007; **6**: 91-96 [PMID: 17224641 DOI: 10.4161/cbt.6.1.3554]
91 **Pandey SN**, Dixit M, Choudhuri G, Mittal B. Lipoprotein receptor associated protein (LRPAP1) insertion/deletion polymorphism: association with gallbladder cancer susceptibility. *Int J Gastrointest Cancer* 2006; **37**: 124-128 [PMID: 17987404 DOI: 10.1007/s12029-007-9002-y]
92 **Singh MK**, Chetri K, Pandey UB, Kapoor VK, Mittal B, Choudhuri G. Mutational spectrum of K-ras oncogene among Indian patients with gallbladder cancer. *J Gastroenterol Hepatol* 2004; **19**: 916-921 [PMID: 15242496 DOI: 10.1111/j.1440-1746.2004.03355.x]
93 **Singh MK**, Pandey UB, Ghoshal UC, Srivenu I, Kapoor VK, Choudhuri G, Mittal B. Apolipoprotein B-100 XbaI gene polymorphism in gallbladder cancer. *Hum Genet* 2004; **114**: 280-283 [PMID: 14618390 DOI: 10.1007/s00439-003-1056-8]
94 **Pandey M**, Sood BP, Shukla RC, Aryya NC, Singh S, Shukla VK. Carcinoma of the gallbladder: role of sonography in diagnosis and staging. *J Clin Ultrasound* 2000; **28**: 227-232 [PMID: 10800001 DOI: 10.1002/(sici)1097-0096(200006)28:5<227::aid-jcu4>3.0.co;2-4]
95 **Agarwal AK**, Kalayarasan R, Singh S, Javed A, Sakhuja P. All cholecystectomy specimens must be sent for histopathology to detect inapparent gallbladder cancer. *HPB (Oxford)* 2012; **14**: 269-273 [PMID: 22404266 DOI: 10.1111/j.1477-2574.2012.00443.x]
96 **Rana C**, Krishnani N, Kumari N. Ultrasound-guided fine needle aspiration cytology of gallbladder lesions: a study of 596 cases. *Cytopathology* 2016; **27**: 398-406 [PMID: 26990137 DOI: 10.1111/cyt.12296]
97 **Yadav R**, Jain D, Mathur SR, Sharma A, Iyer VK. Gallbladder carcinoma: An attempt of WHO histological classification on fine needle aspiration material. *Cytojournal* 2013; **10**: 12 [PMID: 23858322 DOI: 10.4103/1742-6413.113627]
98 **Chandra S**, Chandra H, Shukla SK, Sahu S. Fine-needle aspiration cytology of gallbladder with an attempt of cytomorphological classification. *Cytojournal* 2019; **16**: 1 [PMID: 30820231 DOI: 10.4103/cytojournal.cytojournal_5_18]

99 **Yadav R**, Jain D, Mathur SR, Iyer VK. Cytomorphology of neuroendocrine tumours of the gallbladder. *Cytopathology* 2016; **27**: 97-102 [PMID: 25689921 DOI: 10.1111/cyt.12239]

100 **Kamboj M**, Gandhi JS, Gupta G, Sharma A, Pasricha S, Mehta A, Chandragouda D, Sinha R. Neuroendocrine Carcinoma of Gall Bladder: A Series of 19 Cases with Review of Literature. *J Gastrointest Cancer* 2015; **46**: 356-364 [PMID: 26208508 DOI: 10.1007/s12029-015-9745-9]

101 **Krishnani N**, Shukla S, Jain M, Pandey R, Gupta RK. Fine needle aspiration cytology in xanthogranulomatous cholecystitis, gallbladder adenocarcinoma and coexistent lesions. *Acta Cytol* 2000; **44**: 508-514 [PMID: 10934941 DOI: 10.1159/000328522]

102 **Goyal S**, Prasad G, Chaudhary D, Sakhuja P, Srivastava S, Aggarwal AK. Role of Guided FNA in Gallbladder Cancer: A Retrospective 3-Year Study. *J Cytol* 2023; **40**: 12-18 [PMID: 37179960 DOI: 10.4103/joc.joc_224_21]

103 **Shukla VK**, Pandey M, Kumar M, Sood BP, Gupta A, Aryya NC, Shukla RC, Verma DN. Ultrasound-guided fine needle aspiration cytology of malignant gallbladder masses. *Acta Cytol* 1997; **41**: 1654-1658 [PMID: 9390120 DOI: 10.1159/000333156]

104 **Shukla S**, Krishnani N, Jain M, Pandey R, Gupta RK. Xanthogranulomatous cholecystitis. Fine needle aspiration cytology in 17 cases. *Acta Cytol* 1997; **41**: 413-418 [PMID: 9100775 DOI: 10.1159/000332533]

105 **Shukla PJ**, Barreto SG, Gupta P, Neve R, Ramadwar M, Deodhar K, Mehta S, Shrikhande SV, Mohandas KM. Is there a role for estrogen and progesterone receptors in gall bladder cancer? *HPB (Oxford)* 2007; **9**: 285-288 [PMID: 18345306 DOI: 10.1080/13651820701481489]

106 **Yadav K**, Agarwal P, Kumar M, Gupta S, Mishra M, Maurya MK, Qayoom S, Goel MM. Immunohistochemical appraisal of epithelial mesenchymal transition type III in gall bladder cancer. *Indian J Pathol Microbiol* 2023; **66**: 44-53 [PMID: 36656209 DOI: 10.4103/ijpm.ijpm_876_21]

107 **Jain V**, Akhtar J, Priya R, Sakhuja P, Goyal S, Agarwal AK, Ghose V, Polisetty RV, Sirdeshmukh R, Siraj F, Gautam P. Tissue proteome analysis for profiling proteins associated with lymph node metastasis in gallbladder cancer. *BMC Cancer* 2023; **23**: 402 [PMID: 37142981 DOI: 10.1186/s12885-023-10840-3]

108 **Priya R**, Jain V, Akhtar J, Saklani N, Sakhuja P, Agarwal AK, Polisetty RV, Sirdeshmukh R, Kar S, Gautam P. Proteomic profiling of cell line-derived extracellular vesicles to identify candidate circulatory markers for detection of gallbladder cancer. *Front Oncol* 2022; **12**: 1027914 [PMID: 36505879 DOI: 10.3389/fonc.2022.1027914]

109 **Akhtar J**, Jain V, Kansal R, Priya R, Sakhuja P, Goyal S, Agarwal AK, Ghose V, Polisetty RV, Sirdeshmukh R, Kar S, Gautam P. Quantitative tissue proteome profile reveals neutrophil degranulation and remodeling of extracellular matrix proteins in early stage gallbladder cancer. *Front Oncol* 2022; **12**: 1046974 [PMID: 36686780 DOI: 10.3389/fonc.2022.1046974]

110 **Priya R**, Jain V, Akhtar J, Chauhan G, Sakhuja P, Goyal S, Agarwal AK, Javed A, Jain AP, Polisetty RV, Sirdeshmukh R, Kar S, Gautam P. Plasma-derived candidate biomarkers for detection of gallbladder carcinoma. *Sci Rep* 2021; **11**: 23554 [PMID: 34876625 DOI: 10.1038/s41598-021-02923-7]

111 **Mishra PK**, Saluja SS, Prithiviraj N, Varshney V, Goel N, Patil N. Predictors of curative resection and long term survival of gallbladder cancer - A retrospective analysis. *Am J Surg* 2017; **214**: 278-286 [PMID: 28233537 DOI: 10.1016/j.amjsurg.2017.02.006]

112 **Negi SS**, Singh A, Chaudhary A. Lymph nodal involvement as prognostic factor in gallbladder cancer: location, count or ratio? *J Gastrointest Surg* 2011; **15**: 1017-1025 [PMID: 21487831 DOI: 10.1007/s11605-011-1528-4]

113 **Shah SH**, Gupta N, Gupta G, Mehta A, Singh S. Lymph node micrometastasis in gallbladder cancer. *Indian J Gastroenterol* 2017; **36**: 268-274 [PMID: 28782079 DOI: 10.1007/s12664-017-0775-z]

114 **Balachandran P**, Agarwal S, Krishnani N, Pandey CM, Kumar A, Sikora SS, Saxena R, Kapoor VK. Predictors of long-term survival in patients with gallbladder cancer. *J Gastrointest Surg* 2006; **10**: 848-854 [PMID: 16769541 DOI: 10.1016/j.gassur.2005.12.002]

115 **Gupta A**, Gupta S, Mani R, Durgapal P, Goyal B, Rajput D, Rao S, Dhar P, Gupta M, Kishore S, Kant R. Expression of Human epidermal growth factor receptor 2, Survivin, Enhancer of zeste homolog -2, Cyclooxygenase-2, p53 and p16 molecular markers in Gall bladder carcinoma. *J Carcinog* 2021; **20**: 7 [PMID: 34321957 DOI: 10.4103/jcar.JCar_4_21]

116 **Jain P**, Goyal S, Chauhan G, Majumdar K, Ali S, Sakhuja P, Agarwal AK. HER-2/neu over expression in gall bladder adenocarcinoma: A quest for potential therapeutic target. *Indian J Pathol Microbiol* 2020; **63**: 214-220 [PMID: 32317518 DOI: 10.4103/IJPM.IJPM_664_19]

117 **Halder S**, Kundu S, Chakraborty J, Chakrabarti S. Significance of HER2 and Ki-67 in Preneoplastic Lesions and Carcinoma of Gallbladder. *J Gastrointest Cancer* 2019; **50**: 848-854 [PMID: 30155833 DOI: 10.1007/s12029-018-0162-8]

118 **Kumari S**, Husain N, Agarwal A, Neyaz A, Gupta S, Chaturvedi A, Lohani M, Sonkar AA. Diagnostic Value of Circulating Free DNA Integrity and Global Methylation Status in Gall Bladder Carcinoma. *Pathol Oncol Res* 2019; **25**: 925-936 [PMID: 29376201 DOI: 10.1007/s12253-017-0380-6]

119 **Rajaguru K**, Mehrotra S, Lalwani S, Mangla V, Mehta N, Nundy S. New scoring system for differentiating xanthogranulomatous cholecystitis from gall bladder carcinoma: a tertiary care centre experience. *ANZ J Surg* 2018; **88**: E34-E39 [PMID: 27599003 DOI: 10.1111/ans.13733]

120 **Kumari S**, Tewari S, Husain N, Agarwal A, Pandey A, Singhal A, Lohani M. Quantification of Circulating Free DNA as a Diagnostic Marker in Gall Bladder Cancer. *Pathol Oncol Res* 2017; **23**: 91-97 [PMID: 27475647 DOI: 10.1007/s12253-016-0087-0]

121 **Nigam J**, Chandra A, Kazmi HR, Parmar D, Singh D, Gupta V. Prognostic significance of survivin in resected gallbladder cancer. *J Surg Res* 2015; **194**: 57-62 [PMID: 25472573 DOI: 10.1016/j.jss.2014.07.054]

122 **Nigam J**, Chandra A, Kazmi HR, Parmar D, Singh D, Gupta V, M N. Expression of survivin mRNA in gallbladder cancer: a diagnostic and prognostic marker? *Tumour Biol* 2014; **35**: 9241-9246 [PMID: 24935470 DOI: 10.1007/s13277-014-2200-x]

123 **Ghosh M**, Sakhuja P, Singh S, Agarwal AK. p53 and beta-catenin expression in gallbladder tissues and correlation with tumor progression in gallbladder cancer. *Saudi J Gastroenterol* 2013; **19**: 34-39 [PMID: 23319036 DOI: 10.4103/1319-3767.105922]

124 **Gupta P**, Gupta RK. Preoperative diagnosis of squamous cell carcinoma of the gallbladder by ultrasound-guided aspiration cytology: clinical and cytological findings of nine cases. *J Gastrointest Cancer* 2012; **43**: 638-641 [PMID: 22791136 DOI: 10.1007/s12029-012-9413-2]

125 **Shukla VK**, Gurubachan, Sharma D, Dixit VK, Usha. Diagnostic value of serum CA242, CA 19-9, CA 15-3 and CA 125 in patients with carcinoma of the gallbladder. *Trop Gastroenterol* 2006; **27**: 160-165 [PMID: 17542293]

126 **Arora VK**, Kumar S, Singh N, Bhatia A. Intraoperative bile cytology of the dysplasia-carcinoma in situ sequence of gallbladder carcinoma. *Cancer* 2005; **105**: 277-281 [PMID: 16047358 DOI: 10.1002/cncr.21320]

127 **Batra Y**, Pal S, Dutta U, Desai P, Garg PK, Makharia G, Ahuja V, Pande GK, Sahni P, Chattopadhyay TK, Tandon RK. Gallbladder cancer in India: a dismal picture. *J Gastroenterol Hepatol* 2005; **20**: 309-314 [PMID: 15683437 DOI: 10.1111/j.1440-1746.2005.03576.x]

128 **Chhabra M**, Kalage D, Gupta P, Siddiqui R, Singh S, Yadav TD, Gupta V, Kaman L, Singh H, Irrinki S, Das C, Prakash G, Saikia UN, Nada R, Dutta U, Sandhu MS. Proposal for a new morphological "combined type" of gallbladder cancer: description of radiopathological characteristics and comparison with other morphological types. *Abdom Radiol (NY)* 2024; **49**: 703-709 [PMID: 37973653 DOI:

10.1007/s00261-023-04090-x]
129 **Rana P**, Pruthi H, Gupta P, Chhabra M, Soundararajan R, Singh S, Gulati A, Das CK, Yadav TD, Gupta V, Saikia UN, Dutta U, Sandhu M. Sonographic "Cervix Sign": A New Ancillary Sign of Gallbladder Neck Malignancy. *J Clin Exp Hepatol* 2023; **13**: 972-976 [PMID: 37975041 DOI: 10.1016/j.jceh.2023.05.013]
130 **Patel A**, Singh H, Nair R, Buva D. 50P Ultrasound guided screening of gallbladder cancer in healthy volunteers: A prospective study from Northern India. *Annals of Oncology* 2020; **31**: S260 [DOI: 10.1016/j.annonc.2020.08.028]
131 **Anadure R**, Sreen A, Singh H, Sharma A, Sharma R, Mohimen A, Gupta S. The utility of screening ultrasound in early diagnosis of gall bladder cancer among high-risk population. *Oncol J India* 2021; **5**: 8 [DOI: 10.4103/oji.oji_51_20]
132 **Gupta P**, Dutta U, Rana P, Singhal M, Gulati A, Kalra N, Soundararajan R, Kalage D, Chhabra M, Sharma V, Gupta V, Yadav TD, Kaman L, Irrinki S, Singh H, Sakaray Y, Das CK, Saikia U, Nada R, Srinivasan R, Sandhu MS, Sharma R, Shetty N, Eapen A, Kaur H, Kambadakone A, de Haas R, Kapoor VK, Barreto SG, Sharma AK, Patel A, Garg P, Pal SK, Goel M, Patkar S, Behari A, Agarwal AK, Sirohi B, Javle M, Garcea G, Nervi F, Adsay V, Roa JC, Han HS. Gallbladder reporting and data system (GB-RADS) for risk stratification of gallbladder wall thickening on ultrasonography: an international expert consensus. *Abdom Radiol (NY)* 2022; **47**: 554-565 [PMID: 34851429 DOI: 10.1007/s00261-021-03360-w]
133 **Gupta P**, Marodia Y, Bansal A, Kalra N, Kumar-M P, Sharma V, Dutta U, Sandhu MS. Imaging-based algorithmic approach to gallbladder wall thickening. *World J Gastroenterol* 2020; **26**: 6163-6181 [PMID: 33177791 DOI: 10.3748/wjg.v26.i40.6163]
134 **Kapoor A**, Kapoor A, Mahajan G. Differentiating malignant from benign thickening of the gallbladder wall by the use of acoustic radiation force impulse elastography. *J Ultrasound Med* 2011; **30**: 1499-1507 [PMID: 22039022 DOI: 10.7863/jum.2011.30.11.1499]
135 **Kalage D**, Gupta P, Gulati A, Yadav TD, Gupta V, Kaman L, Nada R, Singh H, Irrinki S, Das C, Dutta U, Sandhu M. Multiparametric MR imaging with diffusion-weighted, intravoxel incoherent motion, diffusion tensor, and dynamic contrast-enhanced perfusion sequences to assess gallbladder wall thickening: a prospective study based on surgical histopathology. *Eur Radiol* 2023; **33**: 4981-4993 [PMID: 36826499 DOI: 10.1007/s00330-023-09455-w]
136 **Singla V**, Agarwal R, Anikhindi SA, Puri P, Kumar M, Ranjan P, Kumar A, Sharma P, Bansal N, Bakshi P, Verma K, Arora A. Role of EUS-FNA for gallbladder mass lesions with biliary obstruction: a large single-center experience. *Endosc Int Open* 2019; **7**: E1403-E1409 [PMID: 31673611 DOI: 10.1055/a-0982-2862]
137 **Kalra N**, Suri S, Gupta R, Natarajan SK, Khandelwal N, Wig JD, Joshi K. MDCT in the staging of gallbladder carcinoma. *AJR Am J Roentgenol* 2006; **186**: 758-762 [PMID: 16498103 DOI: 10.2214/AJR.04.1342]
138 **Kumaran V**, Gulati S, Paul B, Pande K, Sahni P, Chattopadhyay K. The role of dual-phase helical CT in assessing resectability of carcinoma of the gallbladder. *Eur Radiol* 2002; **12**: 1993-1999 [PMID: 12136317 DOI: 10.1007/s00330-002-1440-0]
139 **Soundararajan R**, Vanka S, Gupta P, Chhabra M, Rana P, Gulati A, Das CK, Saikia UN, Yadav TD, Gupta V, Kaman L, Singh H, Irrinki S, Dutta U, Sandhu MS. Gastrointestinal involvement in gallbladder cancer: Computed tomography findings and proposal of a classification system. *Indian J Gastroenterol* 2023; **42**: 708-712 [PMID: 37318744 DOI: 10.1007/s12664-023-01388-y]
140 **Patkar S**, Chaturvedi A, Goel M, Rangarajan V, Sharma A, Engineer R. Role of positron emission tomography-contrast enhanced computed tomography in locally advanced gallbladder cancer. *J Hepatobiliary Pancreat Sci* 2020; **27**: 164-170 [PMID: 31945262 DOI: 10.1002/jhbp.712]
141 **Goel S**, Aggarwal A, Iqbal A, Gupta M, Rao A, Singh S. 18-FDG PET-CT should be included in preoperative staging of gall bladder cancer. *Eur J Surg Oncol* 2020; **46**: 1711-1716 [PMID: 32331985 DOI: 10.1016/j.ejso.2020.04.015]
142 **Shukla PJ**, Barreto SG, Arya S, Shrikhande SV, Hawaldar R, Purandare N, Rangarajan V. Does PET-CT scan have a role prior to radical re-resection for incidental gallbladder cancer? *HPB (Oxford)* 2008; **10**: 439-445 [PMID: 19088931 DOI: 10.1080/13651820802286910]
143 **Goel M**, Tamhankar A, Rangarajan V, Patkar S, Ramadwar M, Shrikhande SV. Role of PET CT scan in redefining treatment of incidental gall bladder carcinoma. *J Surg Oncol* 2016; **113**: 652-658 [PMID: 26847023 DOI: 10.1002/jso.24198]
144 **Kumar R**, Sharma P, Kumari A, Halanaik D, Malhotra A. Role of 18F-FDG PET/CT in detecting recurrent gallbladder carcinoma. *Clin Nucl Med* 2012; **37**: 431-435 [PMID: 22475890 DOI: 10.1097/RLU.0b013e31824d24c4]
145 **Sinha SR**, Prakash P, Singh RK, Sinha DK. Assessment of tumor markers CA 19-9, CEA, CA 125, and CA 242 for the early diagnosis and prognosis prediction of gallbladder cancer. *World J Gastrointest Surg* 2022; **14**: 1272-1284 [PMID: 36504513 DOI: 10.4240/wjgs.v14.i11.1272]
146 **Agrawal S**, Gupta A, Gupta S, Goyal B, Siddeek RAT, Rajput D, Chauhan U, Kishore S, Gupta M, Kant R. Role of carbohydrate antigen 19-9, carcinoembryonic antigen, and carbohydrate antigen 125 as the predictors of resectability and survival in the patients of Carcinoma Gall Bladder. *J Carcinog* 2020; **19**: 4 [PMID: 33033460 DOI: 10.4103/jcar.JCar_10_20]
147 **Bisht N**, Lohia N, Singh S, Sarin A, Mahato A, Paliwal D, Sinha I, Bhatnagar S. Utility of 18-Flurodeoxyglucose Positron Emission Tomography-Computed Tomography ((18) FDG PET-CT) in Gallbladder Cancer: Experience from a Tertiary Care Hospital. *World J Nucl Med* 2023; **22**: 276-283 [PMID: 38152099 DOI: 10.1055/s-0043-1777699]
148 **Gupta P**, Rana P, Ganeshan B, Kalage D, Irrinki S, Gupta V, Yadav TD, Kumar R, Das CK, Gupta P, Endozo R, Nada R, Srinivasan R, Kalra N, Dutta U, Sandhu M. Computed tomography texture-based radiomics analysis in gallbladder cancer: initial experience. *Clin Exp Hepatol* 2021; **7**: 406-414 [PMID: 35402717 DOI: 10.5114/ceh.2021.111173]
149 **Agrawal S**, Lawrence A, Saxena R. Does CA 19-9 Have Prognostic Relevance in Gallbladder Carcinoma (GBC)? *J Gastrointest Cancer* 2018; **49**: 144-149 [PMID: 28105553 DOI: 10.1007/s12029-016-9914-5]
150 **Sharma RK**, Mishra K, Farooqui A, Behari A, Kapoor VK, Sinha N. (1)H nuclear magnetic resonance (NMR)-based serum metabolomics of human gallbladder inflammation. *Inflamm Res* 2017; **66**: 97-105 [PMID: 27770143 DOI: 10.1007/s00011-016-0998-y]
151 **Mondal SK**, Bhattacharjee D, Mandal PK, Biswas S. Histopathological study of gallbladder carcinoma and its mimics with role of carcinoembryonic antigen immunomarker in resolving diagnostic difficulties. *Indian J Med Paediatr Oncol* 2017; **38**: 411-415 [PMID: 29333003 DOI: 10.4103/ijmpo.ijmpo_230_15]
152 **Sureka B**, Singh VP, Rajesh SR, Laroia S, Bansal K, Rastogi A, Bihari C, Bhadoria AS, Agrawal N, Arora A. Computed Tomography (CT) and Magnetic Resonance (MR) Findings in Xanthogranulomatous Cholecystitis: Retrospective Analysis of Pathologically Proven 30 Cases - Tertiary Care Experience. *Pol J Radiol* 2017; **82**: 327-332 [PMID: 28685006 DOI: 10.12659/PJR.901728]
153 **Kalayarasan R**, Javed A, Puri AS, Puri SK, Sakhuja P, Agarwal AK. A prospective analysis of the preoperative assessment of duodenal involvement in gallbladder cancer. *HPB (Oxford)* 2013; **15**: 203-209 [PMID: 23036027 DOI: 10.1111/j.1477-2574.2012.00539.x]
154 **Agarwal AK**, Kalayarasan R, Javed A, Sakhuja P. Mass-forming xanthogranulomatous cholecystitis masquerading as gallbladder cancer. *J Gastrointest Surg* 2013; **17**: 1257-1264 [PMID: 23615807 DOI: 10.1007/s11605-013-2209-2]

155 **Rana S**, Dutta U, Kochhar R, Rana SV, Gupta R, Pal R, Jain K, Srinivasan R, Nagi B, Nain CK, Singh K. Evaluation of CA 242 as a tumor marker in gallbladder cancer. *J Gastrointest Cancer* 2012; **43**: 267-271 [PMID: 21573879 DOI: 10.1007/s12029-011-9288-7]

156 **Kaza RK**, Gulati M, Wig JD, Chawla YK. Evaluation of gall bladder carcinoma with dynamic magnetic resonance imaging and magnetic resonance cholangiopancreatography. *Australas Radiol* 2006; **50**: 212-217 [PMID: 16732816 DOI: 10.1111/j.1440-1673.2006.01564.x]

157 **Pradhan S**, Shukla VK, Agrawal S, Dixit VK, Sharma OP. Sonographic and colour doppler morphology in carcinoma gallbladder. *Indian J Cancer* 2002; **39**: 143-148 [PMID: 12928573]

158 **Agarwal AK**, Kalayarasan R, Javed A, Gupta N, Nag HH. The role of staging laparoscopy in primary gall bladder cancer--an analysis of 409 patients: a prospective study to evaluate the role of staging laparoscopy in the management of gallbladder cancer. *Ann Surg* 2013; **258**: 318-323 [PMID: 23059504 DOI: 10.1097/SLA.0b013e318271497e]

159 **Agrawal S**, Sonawane RN, Behari A, Kumar A, Sikora SS, Saxena R, Kapoor VK. Laparoscopic staging in gallbladder cancer. *Dig Surg* 2005; **22**: 440-445 [PMID: 16479113 DOI: 10.1159/000091447]

160 **Srikanth G**, Kumar A, Khare R, Siddappa L, Gupta A, Sikora SS, Saxena R, Kapoor VK. Should laparoscopic cholecystectomy be performed in patients with thick-walled gallbladder? *J Hepatobiliary Pancreat Surg* 2004; **11**: 40-44 [PMID: 15754045 DOI: 10.1007/s00534-003-0866-3]

161 **Kapoor VK**, Singh R, Behari A, Sharma S, Kumar A, Prakash A, Singh RK, Saxena R. Anticipatory extended cholecystectomy: the 'Lucknow' approach for thick walled gall bladder with low suspicion of cancer. *Chin Clin Oncol* 2016; **5**: 8 [PMID: 26932432 DOI: 10.3978/j.issn.2304-3865.2016.02.07]

162 **Agarwal AK**, Kalayarasan R, Javed A, Sakhuja P. Role of routine 16b1 lymph node biopsy in the management of gallbladder cancer: an analysis. *HPB (Oxford)* 2014; **16**: 229-234 [PMID: 23869478 DOI: 10.1111/hpb.12127]

163 **Ghosh NK**, Rahul R, Singh A, Sharma S, Kumar A, Singh RK, Behari A, Kapoor VK, Saxena R. Retroperitoneal Lymph Node Metastasis in Gallbladder Cancer: As Bad as Distant Metastasis. *South Asian J Cancer* 2022; **11**: 195-200 [PMID: 36588607 DOI: 10.1055/s-0042-1742595]

164 **Aggarwal A**, Goel S, Sayed AI, Goel V, Talwar V, Singh S. Interaortocaval Lymph Node Metastasis in Gall Bladder Cancer: Is It Regional Node or Metastatic Disease? *J Gastrointest Cancer* 2023; **54**: 1252-1260 [PMID: 36729244 DOI: 10.1007/s12029-023-00914-7]

165 **Singh SK**, Talwar R, Kannan N, Tyagi AK, Jaiswal P, Kumar A. Aggressive Surgical Approach for Gallbladder Cancer: a Single-Center Experience from Northern India. *J Gastrointest Cancer* 2015; **46**: 399-407 [PMID: 26410686 DOI: 10.1007/s12029-015-9766-4]

166 **Wagholikar GD**, Behari A, Krishnani N, Kumar A, Sikora SS, Saxena R, Kapoor VK. Early gallbladder cancer. *J Am Coll Surg* 2002; **194**: 137-141 [PMID: 11848630 DOI: 10.1016/S1072-7515(01)01136-X]

167 **Pottakkat B**, Kapoor A, Prakash A, Singh RK, Behari A, Kumar A, Kapoor VK, Saxena R. Evaluation of a prospective surgical strategy of extended resection to achieve R0 status in gall bladder cancer. *J Gastrointest Cancer* 2013; **44**: 33-40 [PMID: 22987147 DOI: 10.1007/s12029-012-9432-z]

168 **Nag HH**, Nekarakanti PK, Sachan A, Nabi P, Tyagi S. Bi-segmentectomy versus wedge hepatic resection in extended cholecystectomy for T2 and T3 gallbladder cancer: A matched case-control study. *Ann Hepatobiliary Pancreat Surg* 2021; **25**: 485-491 [PMID: 34845120 DOI: 10.14701/ahbps.2021.25.4.485]

169 **Tewari M**, Kumar S, Shukla S, Shukla HS. Analysis of wedge resection of gallbladder bed and lymphadenectomy on adequate oncologic clearance for gallbladder cancer. *Indian J Cancer* 2016; **53**: 552-557 [PMID: 28485349 DOI: 10.4103/ijc.IJC_88_17]

170 **Behari A**, Sikora SS, Wagholikar GD, Kumar A, Saxena R, Kapoor VK. Longterm survival after extended resections in patients with gallbladder cancer. *J Am Coll Surg* 2003; **196**: 82-88 [PMID: 12517555 DOI: 10.1016/S1072-7515(02)01611-3]

171 **Jajal V**, Nekarakanti PK, K S, Nag H. Effects of Cystic Duct Margin Involvement on the Survival Rates of Patients With Gallbladder Cancer: A Propensity Score-Matched Case-Control Study. *Cureus* 2023; **15**: e50585 [PMID: 38226074 DOI: 10.7759/cureus.50585]

172 **Pandey D**, Garg PK, Jakhetiya A, Jain N, Rai S. Surgico-pathological Outcomes of 148 Radical Cholecystectomies Using Systematic Regional Lymphadenectomy Protocol: a Retrospective Study. *J Gastrointest Cancer* 2018; **49**: 221-224 [PMID: 29691709 DOI: 10.1007/s12029-018-0106-3]

173 **Goel M**, Pandrowala S, Patel P, Patkar S. Node positivity in T1b gallbladder cancer: A high volume centre experience. *Eur J Surg Oncol* 2022; **48**: 1585-1589 [PMID: 35341609 DOI: 10.1016/j.ejso.2022.03.013]

174 **Agarwal AK**, Mandal S, Singh S, Bhojwani R, Sakhuja P, Uppal R. Biliary obstruction in gall bladder cancer is not sine qua non of inoperability. *Ann Surg Oncol* 2007; **14**: 2831-2837 [PMID: 17632759 DOI: 10.1245/s10434-007-9456-y]

175 **K S**, Jajal VM, Nekarakanti PK, Choudhary D, Nag HH. Gallbladder Cancer With Jaundice: Surgery Versus No Surgery. *Cureus* 2022; **14**: e30594 [PMID: 36420237 DOI: 10.7759/cureus.30594]

176 **Singh S**, Goel S, Aggarwal A, Iqbal A, Hazarika D, Talwar V. Combination of portal vein embolization and neoadjuvant chemotherapy for locally advanced gallbladder cancer requiring extended hepatectomy - A novel approach. *Indian J Gastroenterol* 2021; **40**: 580-589 [PMID: 34966973 DOI: 10.1007/s12664-021-01182-8]

177 **Agarwal AK**, Mandal S, Singh S, Sakhuja P, Puri S. Gallbladder cancer with duodenal infiltration: is it still resectable? *J Gastrointest Surg* 2007; **11**: 1722-1727 [PMID: 17906907 DOI: 10.1007/s11605-007-0320-y]

178 **Sharma A**, Nagar A, Varshney P, Tomar M, Sarin S, Choubey RP, Kapoor VK. Pancreas-preserving limited duodenal resection: Minimizing morbidity without compromising oncological adequacy. *Ann Hepatobiliary Pancreat Surg* 2022; **26**: 149-158 [PMID: 35168204 DOI: 10.14701/ahbps.21-124]

179 **Patkar S**, Patel S, Kazi M, Goel M. Radical surgery for stage IV gallbladder cancers: Treatment strategies in patients with limited metastatic burden. *Ann Hepatobiliary Pancreat Surg* 2023; **27**: 180-188 [PMID: 36882899 DOI: 10.14701/ahbps.22-111]

180 **Agarwal AK**, Javed A, Kalayarasan R, Sakhuja P. Minimally invasive versus the conventional open surgical approach of a radical cholecystectomy for gallbladder cancer: a retrospective comparative study. *HPB (Oxford)* 2015; **17**: 536-541 [PMID: 25727091 DOI: 10.1111/hpb.12406]

181 **Nag HH**, Sachan A, Nekarakanti PK. Laparoscopic versus open extended cholecystectomy with bi-segmentectomy (s4b and s5) in patients with gallbladder cancer. *J Minim Access Surg* 2021; **17**: 21-27 [PMID: 31603079 DOI: 10.4103/jmas.JMAS_98_19]

182 **Palanisamy S**, Patel N, Sabnis S, Palanisamy N, Vijay A, Palanivelu P, Parthasarthi R, Chinnusamy P. Laparoscopic radical cholecystectomy for suspected early gall bladder carcinoma: thinking beyond convention. *Surg Endosc* 2016; **30**: 2442-2448 [PMID: 26416372 DOI: 10.1007/s00464-015-4495-0]

183 **Goel M**, Khobragade K, Patkar S, Kanetkar A, Kurunkar S. Robotic surgery for gallbladder cancer: Operative technique and early outcomes. *J Surg Oncol* 2019; **119**: 958-963 [PMID: 30802316 DOI: 10.1002/jso.25422]

184 **Shukla PJ**, Barreto G, Kakade A, Shrikhande SV. Revision surgery for incidental gallbladder cancer: factors influencing operability and

further evidence for T1b tumours. *HPB (Oxford)* 2008; **10**: 43-47 [PMID: 18695758 DOI: 10.1080/13651820701867794]

185 **Patkar S**, Kunte A, Chaudhari V, Goel M. Outcomes of incidental versus non-incidental T2 gallbladder cancer: A single-institute experience of 425 cases. *J Surg Oncol* 2024; **129**: 754-764 [PMID: 38088226 DOI: 10.1002/jso.27562]

186 **Goel M**, Gupta AM, Patkar S, Parray AM, Shetty N, Ramaswamy A, Patil P, Chopra S, Ostwal V, Kulkarni S, Engineer R, Mehta S. Towards standardization of management of gallbladder carcinoma with obstructive jaundice: Analysis of 113 cases over 10 years at a single institution. *J Surg Oncol* 2021; **124**: 572-580 [PMID: 34106475 DOI: 10.1002/jso.26564]

187 **Patkar S**, Patil V, Acharya MR, Kurunkar S, Goel M. Achieving margin negative resection-doing less is justified: oncological outcomes of wedge excision of liver in gallbladder cancer (GBC) surgery. *Chin Clin Oncol* 2019; **8**: 38 [PMID: 31431034 DOI: 10.21037/cco.2019.07.07]

188 **Nag HH**, Raj P, Sisodia K. The technique of laparoscopic hepatic bisegmentectomy with regional lymphadenectomy for gallbladder cancer. *J Minim Access Surg* 2018; **14**: 124-129 [PMID: 28928327 DOI: 10.4103/jmas.JMAS_181_16]

189 **Kaman L**, Behera A, Singh G, Nedounsejiane M. Radical surgery for incidental cancer gallbladder after laparoscopic cholecystectomy. *Trop Gastroenterol* 2009; **30**: 233-236 [PMID: 20426289]

190 **Patkar S**, Patel S, Gupta A, Ostwal V, Ramaswamy A, Shetty N, Goel M. Lessons learnt from 1300 consecutive gallbladder cancer surgeries: Evolving role of peri-operative chemotherapy in the treatment paradigm. *Eur J Surg Oncol* 2023; **49**: 107035 [PMID: 37604098 DOI: 10.1016/j.ejso.2023.107035]

191 **Ostwal V**, Swami R, Patkar S, Majumdar S, Goel M, Mehta S, Engineer R, Mandavkar S, Kumar S, Ramaswamy A. Gemcitabine-cisplatin (GC) as adjuvant chemotherapy in resected stage II and stage III gallbladder cancers (GBC): a potential way forward. *Med Oncol* 2018; **35**: 57 [PMID: 29564657 DOI: 10.1007/s12032-018-1115-6]

192 **Kattepur AK**, Patkar S, Goel M, Ramaswamy A, Ostwal V. Role of Adjuvant Chemotherapy in Resected T2N0 Gall Bladder Cancer. *J Gastrointest Surg* 2019; **23**: 2232-2238 [PMID: 30706378 DOI: 10.1007/s11605-019-04104-4]

193 **Mahantshetty UM**, Palled SR, Engineer R, Homkar G, Shrivastava SK, Shukla PJ. Adjuvant radiation therapy in gall bladder cancers: 10 years experience at Tata Memorial Hospital. *J Cancer Res Ther* 2006; **2**: 52-56 [PMID: 17998675 DOI: 10.4103/0973-1482.25850]

194 **Choudhary S**, Asthana AK. Impact of Adjuvant Therapy on Survival in Curatively Resected Gallbladder Carcinoma. *J Clin Diagn Res* 2015; **9**: XC01-XC04 [PMID: 26500994 DOI: 10.7860/JCDR/2015/15113.6436]

195 **Agrawal S**, Gupta PK, Rastogi N, Lawrence A, Kumari N, Das KJ, Saxena R. Outcomes of adjuvant chemoradiation and predictors of survival after extended cholecystectomy in gall bladder carcinoma: a single institution experience from an endemic region. *J Gastrointest Cancer* 2015; **46**: 48-53 [PMID: 25511013 DOI: 10.1007/s12029-014-9676-x]

196 **Ramaswamy A**, Ostwal VS, Engineer R, Parulekar M, Mandavkar S, Aier N, Bhargava PG, Srinivas S, Patkar S, Krishnatry R, Gudi S, Kapoor A, Pandey D, Patel S, Shinghal A, Goel A, Dora TK, Chaudhary D, Ankathi SK, Goel M. A multicenter, open-label, randomized phase II study evaluating adjuvant gemcitabine plus cisplatin (GC) and capecitabine with concurrent capecitabine radiotherapy (CAPE-RT) in patients with operated gallbladder adenocarcinoma (GBC): The GECCOR-GB trial. *JCO* 2023; **41**: 4017-4017 [DOI: 10.1200/JCO.2023.41.16_suppl.4017]

197 **Doval DC**, Sekhon JS, Gupta SK, Fuloria J, Shukla VK, Gupta S, Awasthy BS. A phase II study of gemcitabine and cisplatin in chemotherapy-naive, unresectable gall bladder cancer. *Br J Cancer* 2004; **90**: 1516-1520 [PMID: 15083178 DOI: 10.1038/sj.bjc.6601736]

198 **Julka PK**, Puri T, Rath GK. A phase II study of gemcitabine and carboplatin combination chemotherapy in gallbladder carcinoma. *Hepatobiliary Pancreat Dis Int* 2006; **5**: 110-114 [PMID: 16481295]

199 **Ramaswamy A**, Ostwal V, Pinninti R, Kannan S, Bhargava P, Nashikkar C, Mirani J, Banavali S. Gemcitabine-cisplatin versus gemcitabine-oxaliplatin doublet chemotherapy in advanced gallbladder cancers: a match pair analysis. *J Hepatobiliary Pancreat Sci* 2017; **24**: 262-267 [PMID: 28196310 DOI: 10.1002/jhbp.439]

200 **Chatni SS**, Sainani RS, Mehta SA, Mohandas KM. Infusion chemotherapy with cisplatinum and fluorouracil in the treatment of locally-advanced and metastatic gallbladder cancer. *J Cancer Res Ther* 2008; **4**: 151-155 [PMID: 19052386 DOI: 10.4103/0973-1482.43341]

201 **Sharma A**, Dwary AD, Mohanti BK, Deo SV, Pal S, Sreenivas V, Raina V, Shukla NK, Thulkar S, Garg P, Chaudhary SP. Best supportive care compared with chemotherapy for unresectable gall bladder cancer: a randomized controlled study. *J Clin Oncol* 2010; **28**: 4581-4586 [PMID: 20855823 DOI: 10.1200/JCO.2010.29.3605]

202 **Ali D**, Alam N, Yasmin F, Ali S, Anwer T, Alam S, Ahmad S. Comparative Study Between Two Treatment Regimens of Cisplatin-5-Fluorouracil and Gemcitabine-Cisplatin in Gallbladder Cancer Patients. *Iran J Pharm Res* 2017; **16**: 798-804 [PMID: 28979334]

203 **Singh SK**, Talwar R, Kannan N, Tyagi AK, Jaiswal P, Kumar A. Chemotherapy Compared with Best Supportive Care for Metastatic/Unresectable Gallbladder Cancer: a Non-randomized Prospective Cohort Study. *Indian J Surg Oncol* 2016; **7**: 25-31 [PMID: 27065678 DOI: 10.1007/s13193-015-0443-7]

204 **Ramaswamy A**, Ostwal V, Sharma A, Bhargava P, Srinivas S, Goel M, Patkar S, Mandavkar S, Jadhav P, Parulekar M, Choudhari A, Gupta S. Efficacy of Capecitabine Plus Irinotecan *vs* Irinotecan Monotherapy as Second-line Treatment in Patients With Advanced Gallbladder Cancer: A Multicenter Phase 2 Randomized Clinical Trial (GB-SELECT). *JAMA Oncol* 2021; **7**: 436-439 [PMID: 33270098 DOI: 10.1001/jamaoncol.2020.6166]

205 **Alam MN**, Agrawal S, Rastogi N, Saxena R. Chemotherapy or chemotherapy followed by consolidation chemoradiation in postoperative (simple cholecystectomy) gall bladder cancer with residual disease, unsuitable for revision surgery? Risk stratification and outcomes. *J Cancer Res Ther* 2023; **19**: 259-264 [PMID: 37313904 DOI: 10.4103/jcrt.jcrt_1161_21]

206 **Alam MN**, Agrawal S, Rastogi N, Maria Das KJ. Consolidation chemoradiation (cCTRT) improves survival in responders to first-line chemotherapy (CT) in locally advanced gallbladder cancer (LA-GBC): A new standard of care? *Indian J Cancer* 2022; **59**: 577-583 [PMID: 36861528 DOI: 10.4103/ijc.IJC_1145_20]

207 **Das CK**, Patel A, Raj A, Gupta VG, Mehta P, Bhethanabhotla S, Reddy R, Yadav A. Anti-Her2neu directed therapy in advanced gall bladder cancer: A prospective, multicenter experience from India. *JCO* 2020; **38**: e16682-e16682 [DOI: 10.1200/JCO.2020.38.15_suppl.e16682]

208 **Dodagoudar C**, Doval DC, Mahanta A, Goel V, Upadhyay A, Goyal P, Talwar V, Singh S, John MC, Tiwari S, Patnaik N. FOLFOX-4 as second-line therapy after failure of gemcitabine and platinum combination in advanced gall bladder cancer patients. *Jpn J Clin Oncol* 2016; **46**: 57-62 [PMID: 26603355 DOI: 10.1093/jjco/hyv148]

209 **Ramaswamy A**, Ostwal V, Pande N, Sahu A, Jandyal S, Ramadwar M, Shetty N, Patkar S, Goel M, Gupta S. Second-Line Palliative Chemotherapy in Advanced Gall Bladder Cancer, CAP-IRI: Safe and Effective Option. *J Gastrointest Cancer* 2016; **47**: 305-312 [PMID: 27211249 DOI: 10.1007/s12029-016-9828-2]

210 **Gangopadhyay A**, Nath P, Biswas J. Reduced Dose Intensity of Chemotherapy may not Lead to Inferior Palliation in Locally Advanced Carcinoma of the Gall Bladder: An Experience from a Regional Cancer Centre in Eastern India. *J Gastrointest Cancer* 2015; **46**: 297-300

[PMID: 26116258 DOI: 10.1007/s12029-015-9742-z]

211 **Sirohi B**, Rastogi S, Singh A, Sheth V, Dawood S, Talole S, Ramadwar M, Kulkarni S, Shrikhande SV. Use of gemcitabine-platinum in Indian patients with advanced gall bladder cancer. *Future Oncol* 2015; **11**: 1191-1200 [PMID: 25832876 DOI: 10.2217/fon.14.295]

212 **Bhamare S**, Prabhakar P, Dharmadhikari A, Dedeepiya VD, Terunuma H, Senthilkumar R, Srinivasan T, Reena HC, Preethy S, Abraham SJ. Autologous immune enhancement therapy in a case of gall bladder cancer stage IV after surgical resection and chemotherapy yielding a stable non-progressive disease. *J Cancer Res Ther* 2014; **10**: 752-754 [PMID: 25313776 DOI: 10.4103/0973-1482.136048]

213 **Mallick S**, Benson R, Julka PK, Rath GK. Adjuvant chemoradiotherapy for squamous cell carcinoma of gallbladder. *J Gastrointest Cancer* 2014; **45** Suppl 1: 237-240 [PMID: 25119385 DOI: 10.1007/s12029-014-9641-8]

214 **Engineer R**, Wadasadawala T, Mehta S, Mahantshetty U, Purandare N, Rangarajan V, Kishore Shrivastava S. Chemoradiation for unresectable gall bladder cancer: time to review historic nihilism? *J Gastrointest Cancer* 2011; **42**: 222-227 [PMID: 20803101 DOI: 10.1007/s12029-010-9179-3]

215 **Chaudhari VA**, Ostwal V, Patkar S, Sahu A, Toshniwal A, Ramaswamy A, Shetty NS, Shrikhande SV, Goel M. Outcome of neoadjuvant chemotherapy in "locally advanced/borderline resectable" gallbladder cancer: the need to define indications. *HPB (Oxford)* 2018; **20**: 841-847 [PMID: 29706425 DOI: 10.1016/j.hpb.2018.03.008]

216 **Agrawal S**, Mohan L, Mourya C, Neyaz Z, Saxena R. Radiological Downstaging with Neoadjuvant Therapy in Unresectable Gall Bladder Cancer Cases. *Asian Pac J Cancer Prev* 2016; **17**: 2137-2140 [PMID: 27221908 DOI: 10.7314/APJCP.2016.17.4.2137]

217 **Engineer R**, Patkar S, Lewis SC, Sharma AD, Shetty N, Ostwal V, Ramaswamy A, Chopra S, Agrawal A, Patil P, Mehta S, Goel M. A phase III randomised clinical trial of perioperative therapy (neoadjuvant chemotherapy versus chemoradiotherapy) in locally advanced gallbladder cancers (POLCAGB): study protocol. *BMJ Open* 2019; **9**: e028147 [PMID: 31253621 DOI: 10.1136/bmjopen-2018-028147]

218 **Patkar S**, Ostwal V, Ramaswamy A, Engineer R, Chopra S, Shetty N, Dusane R, Shrikhande SV, Goel M. Emerging role of multimodality treatment in gall bladder cancer: Outcomes following 510 consecutive resections in a tertiary referral center. *J Surg Oncol* 2018; **117**: 372-379 [PMID: 28940502 DOI: 10.1002/jso.24837]

219 **Engineer R**, Goel M, Chopra S, Patil P, Purandare N, Rangarajan V, Ph R, Bal M, Shrikhande S, Shrivastava SK, Mehta S. Neoadjuvant Chemoradiation Followed by Surgery for Locally Advanced Gallbladder Cancers: A New Paradigm. *Ann Surg Oncol* 2016; **23**: 3009-3015 [PMID: 27075323 DOI: 10.1245/s10434-016-5197-0]

220 **Sirohi B**, Mitra A, Jagannath P, Singh A, Ramadvar M, Kulkarni S, Goel M, Shrikhande SV. Neoadjuvant chemotherapy in patients with locally advanced gallbladder cancer. *Future Oncol* 2015; **11**: 1501-1509 [PMID: 25963427 DOI: 10.2217/fon.14.308]

221 **Selvakumar VP**, Zaidi S, Pande P, Goel A, Kumar K. Resection after neoadjuvant chemotherapy in advanced carcinoma of the gallbladder: a retrospective study. *Indian J Surg Oncol* 2015; **6**: 16-19 [PMID: 25937758 DOI: 10.1007/s13193-015-0377-0]

World Journal of Clinical Oncology

Submit a Manuscript: https://www.f6publishing.com

World J Clin Oncol 2024 June 24; 15(6): 717-729

DOI: 10.5306/wjco.v15.i6.717

ISSN 2218-4333 (online)

REVIEW

Overview of dyslipidemia and metabolic syndrome in myeloproliferative neoplasms

Mihnea-Alexandru Găman, Bahadar Singh Srichawla, Yong-Feng Chen, Poulami Roy, Arkadeep Dhali, Ahmed Nahian, Muhammad Romail Manan, Vincent Kipkorir, Richard Christian Suteja, Lakshmi Venkata Simhachalam Kutikuppala, Amelia Maria Găman, Camelia Cristina Diaconu

Specialty type: Oncology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification

Scientific Quality: Grade C
Novelty: Grade B
Creativity or Innovation: Grade C
Scientific Significance: Grade B

P-Reviewer: Cigrovski Berkovic M, Croatia

Received: March 12, 2024
Revised: May 5, 2024
Accepted: May 28, 2024
Published online: June 24, 2024
Processing time: 103 Days and 13.5 Hours

Mihnea-Alexandru Găman, Faculty of Medicine, "Carol Davila" University of Medicine and Pharmacy, Bucharest 050474, Romania

Mihnea-Alexandru Găman, Department of Hematology, Center of Hematology and Bone Marrow Transplantation, Fundeni Clinical Institute, Bucharest 022328, Romania

Mihnea-Alexandru Găman, Department of Cellular and Molecular Pathology, Stefan S Nicolau Institute of Virology, Romanian Academy, Bucharest 030304, Romania

Bahadar Singh Srichawla, Department of Neurology, University of Massachusetts Chan Medical School, Worcester, MA 01655, United States

Yong-Feng Chen, Department of Basic Medical Sciences, School of Medicine of Taizhou University, Taizhou University, Taizhou 318000, Zhejiang Province, China

Poulami Roy, Department of Medicine, North Bengal Medical College and Hospital, West Bengal 734012, India

Arkadeep Dhali, Academic Department of Gastroenterology, Sheffield Teaching Hospitals NHS Foundation Trust, Sheffield S5 7AU, United Kingdom

Ahmed Nahian, Lecom at Seton Hill, Greensburg, PA 15601, United States

Muhammad Romail Manan, Faculty of Medicine, Services Hospital, Lahore 54000, Pakistan

Vincent Kipkorir, Department of Human Anatomy and Physiology, University of Nairobi, Nairobi 00100, Kenya

Richard Christian Suteja, Faculty of Medicine, Udayana University, Denpasar, Bali 80361, Indonesia

Lakshmi Venkata Simhachalam Kutikuppala, Department of General Surgery, Dr. NTR University of Health Sciences, Vijayawada 520008, Andhra Pradesh, India

Amelia Maria Găman, Department of Pathophysiology, University of Medicine and Pharmacy of Craiova, Craiova 200349, Romania

Amelia Maria Găman, Clinic of Hematology, Filantropia City Hospital, Craiova 200143, Romania

Camelia Cristina Diaconu, Department of Internal Medicine, Faculty of Medicine, "Carol Davila" University of Medicine and Pharmacy, Bucharest 050474, Romania

Camelia Cristina Diaconu, Internal Medicine Clinic, Clinical Emergency Hospital of Bucharest, Bucharest 105402, Romania

Corresponding author: Amelia Maria Găman, Doctor, MD, PhD, Doctor, Professor, Department of Pathophysiology, University of Medicine and Pharmacy of Craiova, Petru Rareş No. 2, Craiova 200349, Romania. gamanamelia@yahoo.com

Abstract

Myeloproliferative neoplasms (MPNs) occur due to the abnormal proliferation of one or more terminal myeloid cell lines in peripheral blood. Subjects suffering from MPNs display a high burden of cardiovascular risk factors, and thrombotic events are often the cause of death in this population of patients. Herein, we provide a brief overview of dyslipidemia and metabolic syndrome and their epidemiology in MPNs and examine the common molecular mechanisms between dyslipidemia, metabolic syndrome, and MPNs, with a special focus on cardiovascular risk, atherosclerosis, and thrombotic events. Furthermore, we investigate the impact of dyslipidemia and metabolic syndrome on the occurrence and survival of thrombosis in MPN patients, as well as the management of dyslipidemia in MPNs, and the impact of MPN treatment on serum lipid concentrations, particularly as side/adverse effects reported in the context of clinical trials.

Key Words: Polycythemia vera; Essential thrombocythemia; Myelofibrosis; Cardiovascular disease; Hypercholesterolemia; Hypertriglyceridemia; Obesity; Diabetes; Inflammation; Oxidative stress

Core Tip: The topic of dyslipidemia in myeloproliferative neoplasms (MPNs) has only been superficially studied to date. Although it is well known that cardiovascular risk factors impact the management of MPNs and increase the risk of thrombosis which is the main cause of death in MPNs, most investigations have overlooked dyslipidemia as a significant contributor to thrombotic risk and to the risk of death in MPNs. Herein, we provide, to the best of our knowledge, the first overview of lipid abnormalities in MPNs.

Citation: Găman MA, Srichawla BS, Chen YF, Roy P, Dhali A, Nahian A, Manan MR, Kipkorir V, Suteja RC, Simhachalam Kutikuppala LV, Găman AM, Diaconu CC. Overview of dyslipidemia and metabolic syndrome in myeloproliferative neoplasms. *World J Clin Oncol* 2024; 15(6): 717-729
URL: https://www.wjgnet.com/2218-4333/full/v15/i6/717.htm
DOI: https://dx.doi.org/10.5306/wjco.v15.i6.717

INTRODUCTION

Hematopoietic pluripotent stem cells (HPSCs) exhibit a remarkable capacity for self-renewal and undergo differentiation into myeloid or lymphoid lineages. This intricate hematopoietic process culminates in the emergence of various mature blood cells (BCs), which include red BCs (RBCs), lymphocytes, granulocytes, megakaryocytes, and macrophages. The orchestration of hematopoiesis is intricately governed by the complex interplay of the bone marrow microenvironment, growth factors, and transcriptional regulators[1].

Myeloproliferative neoplasms (MPNs) occur due to the abnormal proliferation of one or more terminal myeloid cell lines in peripheral blood. This results in the manifestation of a heterogeneous group of disorders. The initial term "myeloproliferative disorders," originally introduced by William Dameshek in 1951, has been formally standardized and rephrased as "myeloproliferative neoplasms" by the World Health Organization in 2016[2].

Within the classification of MPNs, the updated document encompasses seven distinct subcategories: chronic myeloid leukemia, chronic neutrophilic leukemia, polycythemia vera (PV), primary myelofibrosis (PMF), essential thrombocythemia (ET), chronic eosinophilic leukemia-not otherwise specified and MPN, unclassifiable. Notably, it is imperative to highlight that mastocytosis no longer falls under the MPN category. This revised categorization represents a pivotal advance in the field, indicating a comprehensive and rigorous approach to classifying these complex disorders[2,3].

PV is a chronic myeloproliferative neoplastic disorder characterized by the uncontrolled production of RBCs, resulting in an elevated mass of RBCs. This condition often leads to concurrent stimulation of myeloid and megakaryocytic lineages, leading to increased production of white BCs and platelets. Pathophysiology involves abnormal hematopoietic cell clones with increased sensitivity to growth factors. Signs and symptoms such as headache, dizziness, claudication, and thrombosis arise due to increased blood viscosity. Subjects diagnosed with PV exhibit driver mutations in the Janus kinase 2 (*JAK2*) gene. In > 95% of cases, the *JAK2V617F* mutation is detected in exon 14 of the aforementioned gene, and

the remaining 3%-4% of affected individuals exhibit mutations in exon 12 of the *JAK2* gene[4,5]. Cytogenetic studies reveal abnormal karyotypes in about 34% of patients. PV affects all ethnic groups, with a higher incidence in men, and is usually diagnosed around 60-years-old[6]. In the United States, the overall incidence of PV between 2002 and 2016 was 1.57 (1.55-1.60) per 100000 person years, with fewer cases reported in Japan compared to the United States and Europe[6,7].

ET is another classical BCR-ABL1-negative MPN. It is characterized by excessive platelet production and megakaryocytic hyperplasia in the bone marrow. Initially identified in 1934 under the name "hemorrhagic thrombocythemia", it was subsequently classified as MPN by Damesheck in 1951[8]. About 55% of patients with ET harbor the *JAK2V617F* point mutation[9,10]. ET is related to the development of vascular complications, for example, thrombosis and hemorrhage, which are associated with the presence of thrombocytosis, and there is a possibility of progression of the disease to secondary myelofibrosis (MF)[11,12]. ET is more prevalent among MPNs, affecting 1.0 to 2.5 individuals per 100000 yearly, with a higher incidence in females. The condition becomes more common with age, and most cases present between the ages of 50 and 60[13,14].

PMF is characterized by the clonal overproduction of myeloid cells originating from HPSCs. Although not always present, PMF often involves mutations in the *JAK2*, calreticulin, or myeloproliferative leukemia genes. Additional features include the abnormal presence of collagen fibrosis in the bone marrow, the dysregulated expression of inflammatory cytokines, anemia, hepatosplenomegaly, extramedullary hematopoiesis, constitutional symptoms, cachexia, the risk of progression to acute leukemia, and reduced life expectancy. The incidence of MF in the European Union varies between 0.3 and 1.9 per 100000 people, with an average of 1.1 per 100000[15]. In the United States, the annual incidence of MF is 1.33 per 100000[16]. In high-income countries of the European Union, the prevalence of MF ranges from 0.5 to 9 per 100000 per year[15]. The global prevalence of MF is approximately 1 per 100000 people[16].

BRIEF OVERVIEW OF CARDIOVASCULAR RISK FACTORS IN MPNs

Subjects suffering from MPNs exhibit a high burden of cardiovascular risk factors (CVRFs), thrombotic events often being the cause of death in this patient population[17-19]. In a recent publication by Seguro *et al*[20], the authors conducted a retrospective analysis of hemorrhagic and thrombotic events in a cohort of 334 Brazilian patients with Philadelphia-negative chronic MPNs. The study identified risk factors associated with thrombosis in these patients. The authors of the study used the revised International Prognostic Score in ET to classify patients into four risk categories using four variables: CVRFs, history of thrombosis, age > 60 years, and presence of the *JAK2V617F* mutation. However, CVRFs were not taken into account in the risk assessment of PV and MF in this study. Currently, thrombotic risk in PV is assessed using traditional classification, which classifies individuals as low- or high-risk based on their age (< or > 60 years) and history of thrombosis[20]. In the case of MF, there is currently no validated score to assess thrombotic risk. However, current evidence suggests that one or more CVRF, such as hypertension, diabetes, cigarette smoking, dyslipidemia, or obesity, may increase the risk of thrombosis in MPNs[21]. The previously agreed thrombotic risk classification models for PV and ET introduced an intermediate risk category in addition to the traditional high and low risk categories. This intermediate-risk category included patients under the age of 60 years of age with no history of thrombosis, but with the presence of CVRFs. However, this thrombotic risk classification model is not widely used in clinical practice[22].

Cerquozzi *et al*[23] conducted a study to investigate the association between CVRF and the onset of arterial or venous thrombotic complications in patients with MPNs at or after diagnosis[23]. The findings of their investigation revealed that dyslipidemia, age < 60 years, diabetes, normal karyotype, and hypertension were associated with the development of arterial events. On the other hand, female sex, a history of major hemorrhage, palpable splenomegaly, and age < 60 years were associated with thrombosis in the venous territories[23].

In a recent report by Barbui *et al*[24], hypertension in low-risk patients with PV was emphasized to increase the risk of arterial thrombosis[24]. Currently, for patients with PV or ET who are > 60 years of age and have one or more CVRF, cytoreductive therapy is not recommended. In the revised 2018 management recommendations for classical MPNs negative for BCR-ABL1 issued by European LeukemiaNet, Barbui *et al*[25] argued for the consideration of general risk factors for thrombosis, such as smoking consumption, diabetes mellitus, hypertension and hypercholesterolemia, in the management of MPNs[25].

Accurso *et al*[26] analyzed a cohort of 603 MPN patients who were followed from January 1997 to December 2019 to assess the frequency of CVRF in this population of patients[26]. They investigated the prevalence of smoking, hypertension, diabetes, dyslipidemia, and obesity in different disease subgroups, including 138 cases of overt PMF or post-ET/post-PV MF, 48 cases of prefibrotic PMF, 169 cases of PV, and 249 cases of ET. They also differentiated patients with a single CVRF from those with multiple CVRFs. The overall prevalence of CVRFs in the MPN cohort was 75.95%, with 40.63% of patients having only one CVRF and 35.32% having multiple risk factors. The median age of CVRF patients was 67.57 years, while those without CVRF had a median age of 53.98 years ($P < 0.001$). The high frequency of CVRF in MPNs raises important questions regarding prognosis and therapeutic decisions[26]. However, conclusive data on the impact of CVRFs on thrombotic risk in Philadelphia-negative chronic MPNs are lacking. Prospective studies are needed to determine the risk of thrombotic inflammation in patients with MPNs, both with and without CVRF. If it is demonstrated that CVRFs significantly increase thrombotic risk in MPNs, cytoreductive therapy may be warranted for these individuals. More research is needed to establish the exact relationship between cardiovascular and thrombotic risk in MPNs and inform appropriate therapeutic strategies.

EPIDEMIOLOGY OF DYSLIPIDEMIA IN MPNs AND ITS IMPACT ON THROMBOSIS AND SURVIVAL

Dyslipidemia and metabolic syndrome (MetS) remain some of the most common CVRFs in the general population. Dyslipidemia has traditionally been defined as alterations in serum cholesterol concentrations: total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C) and/or high-density lipoprotein cholesterol (HDL-C) and/or triglycerides (TGs) [27]. However, recent evidence suggests that secondary lipid biomarkers, for example, lipoprotein(a), apolipoproteins, lipid subclasses, and/or subfractions, may provide additional information in terms of cardiovascular risk assessment[27-29]. Furthermore, the MetS which comprises the association in various levels of insulin resistance, hypertension, atherogenic dyslipidemia, and central obesity is also associated with the appearance of cardiovascular events[30].

The interplay of dyslipidemia, MetS, and obesity has been extensively studied not only in the field of cardiology but also by oncology researchers. Metabolic dysfunction has been particularly associated with the development and outcome of a myriad of solid cancers, as well as hematologic malignancies such as lymphoma, multiple myeloma, acute and chronic leukemias, as well as myelodysplastic syndromes and MPNs[31-33]. Furthermore, low concentrations of apolipoprotein A1 (hazard ratio [HR] = 1.59, 95% confidence interval [CI]: 1.22-2.08; $P < 0.001$] and/or high-density lipoprotein cholesterol (HR = 1.66, 95%CI: 1.22-2.26; $P < 0.001$) have been associated with an elevated risk of MPNs even after multiple comparisons were considered[33].

A recent cohort study that evaluated 1537 individuals diagnosed with *JAK2V617F*-positive MPNs reported that dyslipidemia is the second most common CVRF after hypertension in these disorders. Overall, 14.1% of the cases analyzed suffered from hyperlipidemia, which particularly affected PV (16.1%) and PMF (16%) rather than ET subjects (12%). Furthermore, MPN individuals who developed thrombotic events were more frequently described as dyslipidemia compared to those who were thrombosis-free (62.1% *vs* 37.9%; $P < 0.0001$). However, this investigation confirmed CVRFs as predictive factors of thrombotic complications in MPNs[34].

Similarly, Guglielmelli *et al*[35] highlighted that, in their cohort of 382 subjects with prefibrotic PMF, dyslipidemia (12%) was the third most common CVRF after hypertension (27%) and smoking (14%)[35]. Furthermore, dyslipidemia was the CVRF most frequently discovered (16%) after hypertension (42.2%) and diabetes (18.6%) in a cohort of 668 patients with PMF and MF post-PV/post-ET. Furthermore, the authors revealed a negative association between survival and the presence of dyslipidemia in MF (HR = 4.65, 95%CI: 3.11-6.95; $P < 0.001$) in the univariate analysis. However, multivariate Cox proportional hazard models failed to demonstrate their impact on survival[36]. Accurso *et al*[37] also confirmed that dyslipidemia is second among CVRF in people with PV (28.75%) and ET (24.89%) after hypertension based on data derived from a cohort of 403 MPN patients and that CVRFs are associated with an elevated risk of thrombotic events in MPNs[37]. Furthermore, Stein *et al*[38] highlighted that dyslipidemia was notably associated with a history of thrombotic events (odds ratio [OR] = 2.31, 95%CI: 1.00-5.34; $P = 0.05$) in MPN subjects who harbor the *JAK2V617F* mutation[38]. Another assessment indicated that CVRF (obesity, dyslipidemia, diabetes, hypertension, use of cigarettes) are predictors of thrombotic complications after MPN diagnosis (HR = 4.22, 95%CI: 2.00-8.92; $P < 0.001$)[39].

Horvat *et al*[40] analyzed a cohort of 258 MPN individuals who developed arterial and/or venous thrombosis and revealed that dyslipidemia was associated with the development of the aforementioned vascular events (OR = 3.5, 95%CI: 1.8-6.8; $P < 0.001$). However, dyslipidemia was more likely to be associated with the development of arterial (OR = 4.1, 95%CI: 2.0-8.3; $P < 0.001$) rather than venous (OR = 1.5, 95%CI: 0.5-4.5; $P = 0.330$) thrombotic complications[40]. When researchers analyzed thrombotic events by MPN subtype and site of thrombosis, dyslipidemia was only related to arterial but not venous thrombosis in ET (OR = 4.5, 95%CI: 1.6-12.6; $P = 0.006$) and PMF (OR = 6.1, 95%CI: 1.1-33.6; $P = 0.046$)[40]. Furthermore, a Japanese study indicated that elevated serum TG concentrations are positively associated with thrombotic events in ET (HR = 3.530, 95%CI: 1.630-7.643; $P < 0.001$), whereas elevated serum LDL-C concentrations were marginally associated with vascular events in ET (HR = 2.191, 95%CI: 0.966-4.971; $P = 0.061$) in the univariate model. Furthermore, elevated serum TG concentrations were the only CVRF associated with thrombosis in ET (HR = 3.364, 95%CI: 1.541-7.346; $P = 0.002$) in the multivariate model, while the role of elevated serum LDL-C concentrations warrants further investigation (HR = 2.046, 95%CI: 0.895-4.676; $P = 0.09$). More specifically, serum TG concentrations ≥ 106.19 mg/dL were associated with decreased thrombosis-free survival in patients with ET patients (HR = 2.592; $P = 0.026$)[41].

Košťál *et al*[42] analyzed data from the Czech MPN registry to identify risk factors for stroke and/or transient ischemic attack in anagrelide-treated MPNs, revealing that increased serum TC (34.6% *vs* 28.5%) and TG (30.6% *vs* 19.4%) concentrations were more frequent in MPN patients who developed cerebrovascular events *vs* those who did not. However, in the univariate and multivariate analysis, respectively, only hypertriglyceridemia emerged as a notable risk factor for cerebrovascular events (HR = 1.734, 95%CI: 1.162-2.586; $P = 0.008$) whereas hypercholesterolemia did not impact the onset of these complications. Furthermore, hypertriglyceridemia and not hypercholesterolemia remained a significant risk factor for cerebrovascular events even in MPN individuals who did not receive cytoreductive treatment (OR = 2.265, 95%CI: 1.188-4.318; $P = 0.015$)[42].

It is well established that patients with MPNs experience an elevated occurrence of vascular complications. In the largest epidemiological study on PV, CVRFs such as nonhemorrhagic stroke, congestive heart failure, coronary heart disease, and pulmonary embolism contributed to 41% of all deaths[43]. Nonfatal thrombosis occurred at a rate of 3.8 events per year per 100 persons[44]. Similarly, in patients with ET, the rate of thrombosis ranges from 2% to 4% by patients years. One of these thrombotic complications of particular interest due to its severity is splanchnic vein thrombosis. Other microcirculatory thrombosis can also occur that results in vascular headaches, dizziness, visual impairment, distal paresthesia, and erythromelalgia[43].

Multivariate analyses of CVRFs such as dyslipidemia, hypertension, diabetes, and smoking, which investigated the impact on the occurrence of thrombosis in MPNs, have produced conflicting results. Some authors have reported that these risk factors do not influence vascular complications in MPNs, while others propose that the existence of these risks may elevate a low-risk patient to high-risk ED. In the recent International Prognostic Score of ET thrombosis score, the

CVRFs mentioned above were independent variables influencing the rate of thrombosis[43,44]. However, data from a Japanese ET registry that included 1232 subjects of whom 17.6% exhibited elevated LDL-C and 8.4% elevated TG concentrations, respectively, suggests that dyslipidemia is not a predictor of survival in ET, however, hypertriglyceridemia significantly predicted thrombosis-free survival (HR = 3.018, 95%CI: 1.644-5.540; $P < 0.001$). Elevated LDL-C marginally predicted (HR = 1.722, 95%CI: 0.979-3.029; $P = 0.059$) thrombosis-free survival, which warrants investigating this potential thrombotic risk factor in future assessments[45]. CVRFs also appear to be associated with recurrent thrombosis in ET (OR = 3.148, 95%CI: 1.414-7.010; $P = 0.005$); however, the prevalence of dyslipidemia was similar between patients with/without recurrent thrombotic events[46].

Interestingly, in a multicentric Italian cohort that recruited 816 subjects with PV of whom a number of 44 individuals eventually progressed to secondary MF (post-VV), overweight and/or obese PV patients had reduced chances of developing post-VV MF (HR = 0.38, 95%CI = 0.15-0.94; $P = 0.04$) and, in addition, experienced elevated survival rates (HR = 0.42, 95%CI: 0.18-0.97; $P = 0.04$)[47]. However, it seems that MPN patients who also suffer from obesity show an increased burden of symptoms and a reduced quality of life compared to normal weight MPN subjects[48]. This indicates that the perception of people living with MPNs about their quality of life and total symptom burden is also modeled by their cardiovascular comorbidities and increased symptom scores or reduced quality of life scores are not always indicative of disease progression[48,17]. However, Aswad *et al*[49] reported that obesity does not impact the overall rate of thrombotic events or recurrent thrombosis, nor the rates of arterial/vein thrombosis or microvascular disturbances in MPNs and that hereditary thrombophilia is more likely to contribute to the development of thrombotic complications (OR = 2.26; $P = 0.007$) and in particular arterial thrombosis (OR = 2.04; $P = 0.046$) *vs* CVRF[49].

Table 1 summarizes the most relevant findings regarding the interplay between dyslipidemia and/other metabolic disturbances and thrombosis in MPNs.

MANAGEMENT OF DYSLIPIDEMIA AND METABOLIC SYNDROME IN MPNs AND IMPACT OF MPN THERAPY ON THE LIPID PROFILE

Patients with MPNs often have dyslipidemia and MetS, making their management a clinical challenge that requires a comprehensive and integrated approach. Dyslipidemia, characterized by an abnormal lipid profile, typically involves an increase in TC, LDL-C, and TG levels, along with a decrease in HDL-C levels, respectively. Dyslipidemia can contribute to the development of atherosclerosis and increase the risk of cardiovascular disease, and in patients with MPNs, it can trigger the onset of acute coronary syndromes[50,51].

In patients without MPNs, the treatment of dyslipidemia depends on lifestyle modifications, including diet adjustments, increased physical activity, and weight reduction. Currently, pharmacotherapy, primarily with statins, that is β-Hydroxy β-methylglutaryl-CoA reductase inhibitors, is used when lifestyle modifications are not sufficient. For most patients, the goal is to lower LDL-C levels to less than 100 mg/dL, while those at very high cardiovascular risk may need to target an LDL-C level of less than 70 mg/dL[52]. MetS is a cluster of metabolic conditions: elevated blood pressure, central obesity, elevated serum TG, elevated fasting blood glucose, and low HDL-C levels. Each component independently increases the risk of cardiovascular disease, type 2 diabetes, and all-cause mortality[53]. Treatment of MetS involves primarily targeting its components through lifestyle modifications and pharmacotherapy, as required.

The American Diabetes Association and the American Heart Association have established specific goals for metabolic control in patients with MetS. Targets include blood pressure less than 130/80 mmHg, fasting blood glucose less than 100 mg/dL, and hemoglobin levels A1C below 7.0%. Furthermore, the primary objective of treating dyslipidemia as part of MetS is to reduce LDL-C; however, if TG is 200 mg/dL or greater, a secondary goal is to decrease non-HDL-C by 30% to 50% of the baseline of the patient[54].

In the context of patients with MPNs, these metabolic disorders pose unique challenges. *JAK2* gene mutations, a common feature in MPNs, can exacerbate metabolic dysregulation. These mutations are known to activate the JAK/signal transducer and activator of transcription signaling pathway, leading to the proliferation of hematopoietic cells. JAK2 is an essential component of the insulin receptor signaling pathway; upon binding of insulin to its receptor, JAK2 phosphorylates the insulin receptor, leading to downstream signaling events that facilitate glucose uptake[55]. Some studies have demonstrated that carriers of *JAK2* gene mutations show increased insulin, hypoglycemia, and adipose tissue atrophy, reinforcing the link between this mutation and metabolic disorders[56]. Currently, there is growing evidence that *JAK2* gene mutations can lead to altered lipid metabolism due to increased metabolic demand[57,58].

Furthermore, MPNs are associated with a pro-inflammatory state, which could affect insulin sensitivity and lipid metabolism through key homeostatic factors such as adiponectin, which warrants complete metabolic control[59]. Chronic inflammation is believed to contribute to the development of MetS through various mechanisms, including dysregulated adipocytokine production, increased insulin resistance, and direct effects on lipid metabolism[60,61].

MPN-directed therapies can also influence the metabolic profile of these patients. Ruxolitinib, a JAK1/2 inhibitor, is commonly used in the treatment of MPNs. This drug has been associated with weight gain and metabolic changes. Weight gain associated with ruxolitinib is believed to occur due to blocking leptin signaling in the brain leading to increased fat accumulation[62]. Furthermore, Mesa *et al*[63] detected elevated concentrations of TC and LDL-C in patients treated with ruxolitinib compared to pretreatment levels of TC/LDL-C in the same patient cohort[63]. Ruxolitinib has also been shown to increase systolic blood pressure after 72 wk of administration ($P = 0.03$)[64]. This underscores the need for routine metabolic monitoring and personalized therapeutic strategies in patients with MPNs in such therapies. The use of statins is beneficial in patients with MPNs. In a large population-based cohort study involving 876 patients with ET, Podoltsev *et al*[65] demonstrated improved patient survival using statin therapy[65]. Furthermore, a nationwide

Table 1 Relevant results on the interaction between dyslipidemia and other metabolic disturbances and thrombosis or other factors in myeloproliferative neoplasm

Ref.	Study sample	MPN subtypes	Main findings
Pedersen *et al* [33]	116728	Not specified	↓ Apolipoprotein A1 (HR = 1.59, 95%CI: 1.22-2.08; $P < 0.001$) = ↑ risk of MPNs
Pedersen *et al* [33]	116728	Not specified	↓ HDL-C (HR = 1.66, 95%CI: 1.22-2.26; $P < 0.001$) = ↑ risk of MPNs
Zhang *et al* [34]	1537	PV, ET, PMF	↑ Rates of dyslipidemia in MPNs individuals with thrombotic events *vs* thrombosis-free (62.1% *vs* 37.9%; $P < 0.0001$)
García-Fortes et al[36]	668	PMF, post-PV MF, post-ET MF	Negative association of survival and dyslipidemia in MF (HR = 4.65, 95%CI: 3.11-6.95; $P < 0.001$)
Stein *et al*[38]	164	PV, ET, PMF	Association of dyslipidemia and history of thrombotic events (OR = 2.31, 95%CI: 1.00-5.34; $P = 0.05$) in *JAK2V617F*-positive MPNs
Gu *et al*[39]	567	PV	CVRFs (including dyslipidemia) = predictors of thrombosis after MPN diagnosis (HR = 4.22, 95%CI: 2.00-8.92; $P < 0.001$)
Horvat *et al* [40]	258	PV, ET, PMF	Association between dyslipidemia and vascular events (OR = 3.5, 95%CI: 1.8-6.8; $P < 0.001$), arterial thrombosis (OR = 4.1, 95%CI: 2.0-8.3; $P < 0.001$), venous thrombosis (OR = 1.5, 95%CI: 0.5-4.5; $P = 0.330$), arterial thrombosis in ET (OR = 4.5, 95%CI: 1.6-12.6; $P = 0.006$), and PMF (OR = 6.1, 95%CI: 1.1-33.6; $P = 0.046$)
Furuya *et al* [41]	580	ET	↑ TG positively associated with thrombotic events in ET (HR = 3.530, 95%CI: 1.630-7.643; $P < 0.001$)
Furuya *et al* [41]	580	ET	LDL-C concentrations marginally associated with vascular events in ET (HR = 2.191, 95%CI: 0.966-4.971; $P = 0.061$)
Furuya *et al* [41]	580	ET	↑ TG = only CVRF associated with thrombosis in ET (HR = 3.364, 95%CI: 1.541-7.346; $P = 0.002$)
Furuya *et al* [41]	580	ET	TG ≥ 106.19 mg/dL = ↓ thrombosis-free survival in ET (HR = 2.592; P = 0.026)
Košťál *et al* [42]	1142	PV, ET, PMF	Hypertriglyceridemia not hypercholesterolemia = RF for cerebrovascular events (HR = 1.734, 95%CI: 1.162-2.586; $P = 0.008$)
Košťál *et al* [42]	1142	PV, ET, PMF	Hypertriglyceridemia and not hypercholesterolemia = RF for cerebrovascular events in MPNs without cytoreductive treatment (OR = 2.265, 95%CI: 1.188-4.318; $P = 0.015$)
Hashimoto *et al*[45]	1152	ET	Hypertriglyceridemia predicts thrombosis-free survival (HR = 3.018, 95%CI: 1.644-5.540; $P < 0.001$)
Hashimoto *et al*[45]	1152	ET	↑ LDL-C marginally predicts thrombosis-free survival (HR = 1.722, 95%CI: 0.979-3.029; $P = 0.059$)
Benevolo *et al* [47]	816	PV	overweight/obese PV = ↓ post-PV MF rates (HR = 0.38, 95%CI = 0.15-0.94; $P = 0.04$)
Benevolo *et al* [47]	816	PV	overweight/obese PV = ↑ survival rates (HR = 0.42, 95%CI: 0.18-0.97; $P = 0.04$)
Christensen *et al*[48]	3114	PV, ET, PMF	obesity + MPNs = ↑ symptom burden & ↓ QoL *vs* normal-weight MPNs

CI: Confidence interval; CVRFs: Cardiovascular risk factors; ET: Essential thrombocythemia; HDL-C: High-density lipoprotein cholesterol; HR: Hazard ratio; MF: Myelofibrosis; MPNs: Myeloproliferative neoplasms; OR: Odds ratio; PMF: Primary myelofibrosis; PV: Polycythemia vera; QoL: Quality of life; RF: Risk factor; ↑ increased/elevated; ↓: Reduced/decreased.

Danish case-control study demonstrated lower odds of being diagnosed with MPNs among statin users, alluding to the possible anti-neoplastic mechanisms of statin drugs[66]. The intricate interplay between MPNs, dyslipidemia, and MetS underscores the need for a comprehensive, multipronged approach to patient management. As our understanding of the biological connections between these conditions expands, we can expect to refine our therapeutic strategies further, ultimately improving patient outcomes.

Although the main objective of MPN treatment is to control the overproduction of one or more types of BCs, emerging research has shown that MPN treatments can have unintended impacts on serum lipid concentrations of patients, potentially leading to dyslipidemia and MetS[67]. Dyslipidemia, a condition characterized by an abnormal amount of lipids in the blood, and MetS, a group of conditions including increased blood pressure, high blood sugar, excess body fat around the waist, and abnormal TC or TG levels, have been increasingly reported as side effects of various MPN treatments. These adverse effects can significantly affect the quality of life of patients, and if left untreated, they can contribute to the development of cardiovascular disease, a leading cause of death among patients with MPNs[68]. An

investigation led by Sung *et al*[69] reported that patients treated with ruxolitinib exhibited increased levels of LDL-C and decreased levels of HDL-C, a lipid profile commonly associated with an increased risk of atherosclerotic cardiovascular disease[69]. Interferon-alpha, another treatment prescribed for MPNs, has also been shown to induce changes in lipid profiles. Sun *et al*[70] observed that treatment with pegylated interferon-alpha resulted in lower HDL-C levels in patients with PV, supporting the hypothesis that interferon-alpha may lead to dyslipidemia and therefore increase cardiovascular risk in MPN patients[70].

It is important to note that MPN patients are already at increased risk of thrombosis due to the nature of the disease itself, and the addition of dyslipidemia and MetS can exacerbate this risk. The interplay between MPN treatment, lipid metabolism, and cardiovascular risk is complex and multifaceted. For example, MPN treatments may influence MetS development by inducing weight gain, a common side effect of JAK inhibitors such as ruxolitinib[62]. Furthermore, patients with MPNs often present with inflammation, which can also contribute to dyslipidemia and MetS. Chronic inflammation has been associated with insulin resistance, which is a key driver of MetS. MPN treatments such as ruxolitinib have potent anti-inflammatory effects, but can also affect metabolic homeostasis, leading to adverse metabolic effects[71].

Although these potential side effects are concerning, it is important to note that the benefits of MPN therapy, including control of disease symptoms and improvement in survival, often outweigh these risks. However, these findings highlight the need for regular monitoring of serum lipid profiles and metabolic parameters in patients undergoing MPN treatment. They also emphasize the importance of lifestyle modifications, including diet and physical activity, to counteract these potential side effects. It is crucial that clinicians consider the possible impact of MPN treatments on serum lipid concentrations, dyslipidemia, and MetS. By closely monitoring these parameters, early intervention and educating patients about lifestyle changes, clinicians can help mitigate the risk of cardiovascular disease and improve the overall quality of life for patients with MPNs.

MOLECULAR MECHANISMS COMMON IN DYSLIPIDEMIA, METS AND MPNs

Clonal hematopoiesis is the process of equipotential cloning of hematopoietic stem cells (HSCs) with the aim of providing the body with a sufficient number of HSCs, therefore regulating the amount of its derivatives within the body[72,73]. The process is similar to that of regular cell division. However, since gene replication is prone to errors due to DNA derangement and telomere shortening, the fact that cells with higher potency offer a larger range of expressed genes means that any mutations within the replicated DNA will be expressed more frequently[73,74]. At the same time, telomere shortening reduces the production of enzymes that delay cell senescence, apoptosis, and decrease susceptibility to genetic mutations[75-78]. Researchers reported a correlation between telomere shortening and decline in stem cell function as people age[75,76]. Another study inversely proved that mice overexpressing telomeres showed that mice with longer telomeres had delayed aging and increased cancer resistance[79].

As cells are always exposed to the environment, they continuously accumulate oxidative stress throughout their life [73]. Derangement may then be passed on to the next generation of cells: Causing transcription, translation, and proofreading to fail during DNA synthesis. This perpetuates to form a cycle where cells live to continuously accumulate derangements, only to be passed on later to the next generation of cells[73]. This explains why 'degenerative' diseases become more apparent as we age[73]. This process is called a somatic mutation, described as cellular level alteration in somatic tissues occurring after fertilization that does not involve the germline and consequently does not carry on to the offspring[80].

Exploring the root cause of DNA damage further, scientists have discovered that oxidative stress played a key role in causing derangements of the molecular composition within amino acids that form the DNA chain[80,81]. Oxidative stress occurs due to an imbalance between reactive oxygen and nitrogen species and antioxidants within the body[80-82]. It may be obtained internally as a byproduct of metabolism (which includes pathogen-caused inflammation) and externally from the environment. Eventually, these mutations can evolve from silent mutations into diseases deemed clinically significant [80-82].

However, the occurrence of thrombotic events, particularly in young people, should warrant screening for blood cancers and especially MPNs. Mayerhofer *et al*[83] highlighted that young individuals who experience episodes of stroke display a three-times elevated prevalence of clonal hematopoiesis of indeterminate potential mutations and several suffer from MPNs and eventually need of cytoreduction treatment. Furthermore, they defined that these patients express a higher burden of atherosclerosis and an elevated carotid intima media thickness, reinforcing that there is pronounced endothelial dysfunction in MPNs[83,84]. It is well known that dyslipidemia aggravates atherogenesis and is associated with inflammation, oxidative stress, cytokines, and other molecular messengers to promote atherosclerosis, including in subjects with MPNs[85-87]. We have learned from murine models that laboratory mice that express the *JAK2V617F* mutation and suffer from dyslipidemia exhibit a myriad of aberrant molecular mechanisms that aggravate atherosclerosis, namely macrophage erythrophagocytosis, increased lipid peroxidation, p38 mitogen-activated protein kinase signaling and concentrations of pro-inflammatory chemokines, RBC-derived microvesicles and cytokines, endothelial damage, defective efferocytosis, inflammasome overactivation, ferroptosis, decreased levels of c-Mer tyrosine kinase, and expansion of preleukemic HSCs[88-91]. ATP-binding cassette sub-family G member 1 and ATP binding cassette subfamily A member 1, *i.e.* adenosine triphosphate-binding cassette transporters, N-acetyl cysteine, fedratinib, HDL-C, and simvastatin seem to alleviate atherogenesis, myelopoiesis, and endothelial dysfunction in *in vivo* assessments of *JAK2V617F*-positive mice[90,92,93]. These findings have been confirmed by investigations conducted in MPN subjects, as Skov *et al*[94] pointed out that in MPNs, there is a dysregulation of several genes involved in the development of athero-

sclerosis, for example downregulation of B-cell lymphoma 2 (Bcl-2) and upregulation of matrix metalloproteinase 1, Bcl-2-like protein 1, thrombospondin-4, and prostaglandin-endoperoxide synthase 1 is in PV, ET, and PMF[94]. Moreover, elevated variant allele frequencies of *JAK2V617F* and neutrophil-to-lymphocyte ratios are associated with notable inflammation, arterial stiffness, and atherosclerosis in MPNs[95-97]. Furthermore, in subjects with atherosclerosis, dyslipidemia is associated with increased concentrations of platelet-derived growth factor and other cytokines which are molecules known to stimulate proliferation of myeloid cells, and peripheral arterial disease, a vascular complication driven by lipid abnormalities and atherogenesis, has been shown along with atrial fibrillation to be a notable predictor of thrombotic and bleeding complications, as well as death in MPNs[98,99]. Thus, the crosstalk between dyslipidemia, inflammation, and oxidative stress may stimulate a process of accelerated atherosclerosis in MPNs and eventually results in higher rates of thrombotic and, in some cases, hemorrhagic complications in these hematological malignancies (Figure 1)[100].

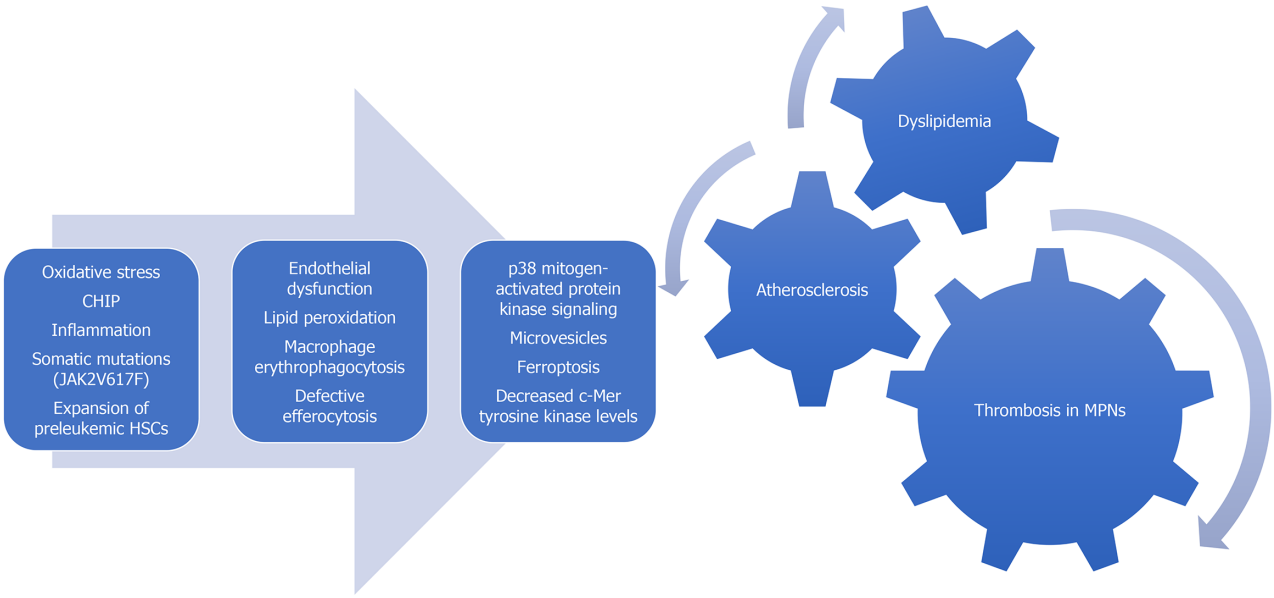


Figure 1 Schematic representation of the interplay among dyslipidemia, atherosclerosis, and myeloproliferative neoplasms, with a focus on the main pathogenetic mechanisms that drive the development of atherosclerosis. CHIP: Clonal hematopoiesis of indeterminate potential; HSC: Hematopoietic stem cells; MPNs: Myeloproliferative neoplasms.

CONCLUSION

Lipid abnormalities trigger the development of atherosclerosis and work together with oxidative stress, inflammation, genetics, and a conundrum of molecules to increase the risk of thrombosis in MPNs. In addition, several drugs used in the treatment of these blood cancers, such as ruxolitinib or interferon-alpha, may alter the lipid profiles of MPN subjects. Thus, the interaction between dyslipidemia and MPNs appears complex and requires in-depth research in future studies that should evaluate the impact of dyslipidemia as a unique and potentially deleterious CVRF in these hematologic malignancies.

FOOTNOTES

Author contributions: Găman MA contributed to the study conceptualization, data curation, funding acquisition, methodology, resources, validation, visualization, and software; Găman MA, Srichawla BS, Chen YF, Roy P, Dhali A, Nahian A, Manan MR, Kipkorir V, Suteja RC, and Simhachalam Kutikuppala LV contributed to the formal analysis, investigation, and writing of the original draft; Găman MA, Găman AM, and Diaconu CC contributed to the project administration and supervision; Găman MA, Srichawla BS, Găman AM, and Diaconu CC contributed to the writing, review, and editing.

Supported by the Grant Funded by Competitiveness Operational Programme A1.1.4. ID: P_37_798 MYELOAL-EDIAPROT (to Găman MA), No. 149/26.10.2016 (MySMIS2014+: 106774).

Conflict-of-interest statement: Dr. Găman reports grants from the Competitiveness Operational Programme A1.1.4. ID: P_37_798 MYELOAL-EDIAPROT, Grant Agreement No. 149/26.10.2016 (MySMIS2014+: 106774), during the conduct of the study. The other authors do not have any conflicts of interest to declare.

Country of origin: Romania

ORCID number: Mihnea-Alexandru Găman 0000-0001-7133-8875; Bahadar Singh Srichawla 0000-0002-5301-4102; Arkadeep Dhali 0000-0002-1794-2569; Muhammad Romail Manan 0000-0002-3436-5206; Vincent Kipkorir 0000-0001-6946-8857; Lakshmi Venkata Simhachalam Kutikuppala 0000-0002-5685-6049; Amelia Maria Găman 0000-0001-6974-2772; Camelia Cristina Diaconu 0000-0001-6837-260X.

Corresponding Author's Membership in Professional Societies: Romanian Society of Hematology; Romanian Society of Pathophysiology; Romanian College of Physicians; International Society of Pathophysiology.

S-Editor: Li L
L-Editor: Filipodia
P-Editor: Zhao YQ

REFERENCES

1 **Ghiaur G**, Jones RJ. Hematopoiesis. *Concise Guide to Hematology* 2019 [DOI: 10.1007/978-3-319-97873-4_2]
2 **Barbui T**, Thiele J, Gisslinger H, Kvasnicka HM, Vannucchi AM, Guglielmelli P, Orazi A, Tefferi A. The 2016 WHO classification and diagnostic criteria for myeloproliferative neoplasms: document summary and in-depth discussion. *Blood Cancer J* 2018; **8**: 15 [PMID: 29426921 DOI: 10.1038/s41408-018-0054-y]
3 **Găman MA**, Cozma MA, Dobrică EC, Crețoiu SM, Găman AM, Diaconu CC. Liquid Biopsy and Potential Liquid Biopsy-Based Biomarkers in Philadelphia-Negative Classical Myeloproliferative Neoplasms: A Systematic Review. *Life (Basel)* 2021; **11** [PMID: 34357048 DOI: 10.3390/life11070677]
4 **Easwar A**, Siddon AJ. Genetic Landscape of Myeloproliferative Neoplasms with an Emphasis on Molecular Diagnostic Laboratory Testing. *Life (Basel)* 2021; **11** [PMID: 34833034 DOI: 10.3390/life11111158]
5 **Barbui T**, Barosi G, Birgegard G, Cervantes F, Finazzi G, Griesshammer M, Harrison C, Hasselbalch HC, Hehlmann R, Hoffman R, Kiladjian JJ, Kröger N, Mesa R, McMullin MF, Pardanani A, Passamonti F, Vannucchi AM, Reiter A, Silver RT, Verstovsek S, Tefferi A; European LeukemiaNet. Philadelphia-negative classical myeloproliferative neoplasms: critical concepts and management recommendations from European LeukemiaNet. *J Clin Oncol* 2011; **29**: 761-770 [PMID: 21205761 DOI: 10.1200/JCO.2010.31.8436]
6 **Verstovsek S**, Yu J, Scherber RM, Verma S, Dieyi C, Chen CC, Parasuraman S. Changes in the incidence and overall survival of patients with myeloproliferative neoplasms between 2002 and 2016 in the United States. *Leuk Lymphoma* 2022; **63**: 694-702 [PMID: 34689695 DOI: 10.1080/10428194.2021.1992756]
7 **Johansson P**. Epidemiology of the myeloproliferative disorders polycythemia vera and essential thrombocythemia. *Semin Thromb Hemost* 2006; **32**: 171-173 [PMID: 16673273 DOI: 10.1055/s-2006-939430]
8 **Cervantes F**. Management of essential thrombocythemia. *Hematology Am Soc Hematol Educ Program* 2011; **2011**: 215-221 [PMID: 22160037 DOI: 10.1182/asheducation-2011.1.215]
9 **Tefferi A**, Pardanani A. Myeloproliferative Neoplasms: A Contemporary Review. *JAMA Oncol* 2015; **1**: 97-105 [PMID: 26182311 DOI: 10.1001/jamaoncol.2015.89]
10 **Torres DG**, Paes J, da Costa AG, Malheiro A, Silva GV, Mourão LPS, Tarragô AM. JAK2 Variant Signaling: Genetic, Hematologic and Immune Implication in Chronic Myeloproliferative Neoplasms. *Biomolecules* 2022; **12** [PMID: 35204792 DOI: 10.3390/biom12020291]
11 **Moisa C**, Gaman MA, Diaconu CC, Gaman AM. Oxidative Stress Levels, JAK2V617F Mutational Status and Thrombotic Complications in Patients with Essential Thrombocythemia. *Rev Chim* 2019; **70**: 2822-2825 [DOI: 10.37358/RC.19.8.7435]
12 **Wang D**, Yu X, Sun Y, Lv Y, Li Y, Zhao P, Niu J, Zhang Y, Chen Y, Chen K, Chen Z, Liu W, Wang M, Hu X. Incidence of Thrombosis at Different Sites During the Follow-Up Period in Essential Thrombocythemia: A Systematic Review and Meta-Analysis. *Clin Appl Thromb Hemost* 2023; **29**: 10760296231181117 [PMID: 37350087 DOI: 10.1177/10760296231181117]
13 **Meier B**, Burton JH. Myeloproliferative Disorders. *Hematol Oncol Clin North Am* 2017; **31**: 1029-1044 [PMID: 29078922 DOI: 10.1016/j.hoc.2017.08.007]
14 **Mehta J**, Wang H, Iqbal SU, Mesa R. Epidemiology of myeloproliferative neoplasms in the United States. *Leuk Lymphoma* 2014; **55**: 595-600 [PMID: 23768070 DOI: 10.3109/10428194.2013.813500]
15 **Moulard O**, Mehta J, Fryzek J, Olivares R, Iqbal U, Mesa RA. Epidemiology of myelofibrosis, essential thrombocythemia, and polycythemia vera in the European Union. *Eur J Haematol* 2014; **92**: 289-297 [PMID: 24372927 DOI: 10.1111/ejh.12256]
16 **Hoffman R**, Benz EJ, Silberstein LE, Heslop H, Weitz J, Salama ME, Abutalib SA. Hematology: Basic principles and practice. 8th. Philadelphia, PA: Elsevier, 2018
17 **Găman MA**, Kipkorir V, Srichawla BS, Dhali A, Găman AM, Diaconu CC. Primary Arterial Hypertension and Drug-Induced Hypertension in Philadelphia-Negative Classical Myeloproliferative Neoplasms: A Systematic Review. *Biomedicines* 2023; **11** [PMID: 36830925 DOI: 10.3390/biomedicines11020388]
18 **Hultcrantz M**, Wilkes SR, Kristinsson SY, Andersson TM, Derolf ÅR, Eloranta S, Samuelsson J, Landgren O, Dickman PW, Lambert PC, Björkholm M. Risk and Cause of Death in Patients Diagnosed With Myeloproliferative Neoplasms in Sweden Between 1973 and 2005: A Population-Based Study. *J Clin Oncol* 2015; **33**: 2288-2295 [PMID: 26033810 DOI: 10.1200/JCO.2014.57.6652]
19 **Găman MA**, Cozma MA, Manan MR, Srichawla BS, Dhali A, Ali S, Nahian A, Elton AC, Simhachalam Kutikuppala LV, Suteja RC, Diebel S, Găman AM, Diaconu CC. Budd-Chiari syndrome in myeloproliferative neoplasms: A review of literature. *World J Clin Oncol* 2023; **14**: 99-116 [PMID: 37009527 DOI: 10.5306/wjco.v14.i3.99]

20 **Seguro FS**, Teixeira LLC, da Rosa LI, da Silva WF, Nardinelli L, Bendit I, Rocha V. Risk factors and incidence of thrombosis in a Brazilian cohort of patients with Philadelphia-negative myeloproliferative neoplasms. *J Thromb Thrombolysis* 2020; **49**: 667-672 [PMID: 31898273 DOI: 10.1007/s11239-019-02029-y]

21 **Moisă C**, Găman M, Assani AD, Găman A. The evaluation of oxidative stress in patients with essential thrombocythemia treated with risk-adapted therapy. *Arch Balk Med Union* 2018; **53**: 529-534 [DOI: 10.31688/ABMU.2018.53.4.07]

22 **Finazzi G**, Barbui T. Risk-adapted therapy in essential thrombocythemia and polycythemia vera. *Blood Rev* 2005; **19**: 243-252 [PMID: 15963833 DOI: 10.1016/j.blre.2005.01.001]

23 **Cerquozzi S**, Barraco D, Lasho T, Finke C, Hanson CA, Ketterling RP, Pardanani A, Gangat N, Tefferi A. Risk factors for arterial *vs* venous thrombosis in polycythemia vera: a single center experience in 587 patients. *Blood Cancer J* 2017; **7**: 662 [PMID: 29282357 DOI: 10.1038/s41408-017-0035-6]

24 **Barbui T**, Masciulli A, Ghirardi A, Carobbio A. ACE inhibitors and cytoreductive therapy in polycythemia vera. *Blood* 2017; **129**: 1226-1227 [PMID: 28028024 DOI: 10.1182/blood-2016-11-752600]

25 **Barbui T**, Tefferi A, Vannucchi AM, Passamonti F, Silver RT, Hoffman R, Verstovsek S, Mesa R, Kiladjian JJ, Hehlmann R, Reiter A, Cervantes F, Harrison C, Mc Mullin MF, Hasselbalch HC, Koschmieder S, Marchetti M, Bacigalupo A, Finazzi G, Kroeger N, Griesshammer M, Birgegard G, Barosi G. Philadelphia chromosome-negative classical myeloproliferative neoplasms: revised management recommendations from European LeukemiaNet. *Leukemia* 2018; **32**: 1057-1069 [PMID: 29515238 DOI: 10.1038/s41375-018-0077-1]

26 **Accurso V**, Santoro M, Mancuso S, Siragusa S. Cardiovascular risk factor in MPN patients. *J Thromb Thrombolysis* 2020; **50**: 640-641 [PMID: 32002767 DOI: 10.1007/s11239-020-02049-z]

27 **Berberich AJ**, Hegele RA. A Modern Approach to Dyslipidemia. *Endocr Rev* 2022; **43**: 611-653 [PMID: 34676866 DOI: 10.1210/endrev/bnab037]

28 **Santos HO**, Kones R, Rumana U, Earnest CP, Izidoro LFM, Macedo RCO. Lipoprotein(a): Current Evidence for a Physiologic Role and the Effects of Nutraceutical Strategies. *Clin Ther* 2019; **41**: 1780-1797 [PMID: 31307832 DOI: 10.1016/j.clinthera.2019.06.002]

29 **Santos HO**, Earnest CP, Tinsley GM, Izidoro LFM, Macedo RCO. Small dense low-density lipoprotein-cholesterol (sdLDL-C): Analysis, effects on cardiovascular endpoints and dietary strategies. *Prog Cardiovasc Dis* 2020; **63**: 503-509 [PMID: 32353373 DOI: 10.1016/j.pcad.2020.04.009]

30 **Fahed G**, Aoun L, Bou Zerdan M, Allam S, Bouferraa Y, Assi HI. Metabolic Syndrome: Updates on Pathophysiology and Management in 2021. *Int J Mol Sci* 2022; **23** [PMID: 35054972 DOI: 10.3390/ijms23020786]

31 **Karra P**, Winn M, Pauleck S, Bulsiewicz-Jacobsen A, Peterson L, Coletta A, Doherty J, Ulrich CM, Summers SA, Gunter M, Hardikar S, Playdon MC. Metabolic dysfunction and obesity-related cancer: Beyond obesity and metabolic syndrome. *Obesity (Silver Spring)* 2022; **30**: 1323-1334 [PMID: 35785479 DOI: 10.1002/oby.23444]

32 **Bilgihan MT**, Ciftciler R. The Effect of Obesity and Body Mass Index on Hematologic Malignancies. *Metab Syndr Relat Disord* 2023; **21**: 353-361 [PMID: 37410513 DOI: 10.1089/met.2023.0048]

33 **Pedersen KM**, Çolak Y, Bojesen SE, Nordestgaard BG. Low high-density lipoprotein and increased risk of several cancers: 2 population-based cohort studies including 116,728 individuals. *J Hematol Oncol* 2020; **13**: 129 [PMID: 32998735 DOI: 10.1186/s13045-020-00963-6]

34 **Zhang Y**, Zhou Y, Wang Y, Teng G, Li D, Du C, Chen Y, Zhang H, Li Y, Fu L, Chen K, Bai J. Thrombosis among 1537 patients with JAK2(V617F) -mutated myeloproliferative neoplasms: Risk factors and development of a predictive model. *Cancer Med* 2020; **9**: 2096-2105 [PMID: 31994332 DOI: 10.1002/cam4.2886]

35 **Guglielmelli P**, Carobbio A, Rumi E, De Stefano V, Mannelli L, Mannelli F, Rotunno G, Coltro G, Betti S, Cavalloni C, Finazzi MC, Thiele J, Cazzola M, Vannucchi AM, Barbui T. Validation of the IPSET score for thrombosis in patients with prefibrotic myelofibrosis. *Blood Cancer J* 2020; **10**: 21 [PMID: 32098944 DOI: 10.1038/s41408-020-0289-2]

36 **García-Fortes M**, Hernández-Boluda JC, Álvarez-Larrán A, Raya JM, Angona A, Estrada N, Fox L, Cuevas B, García-Hernández MC, Gómez-Casares MT, Ferrer-Marín F, Saavedra S, Cervantes F, García-Delgado R, On Behalf Of The Grupo Español de Enfermedades Mieloproliferativas Filadelfia Negativas Gemfin. Impact of Individual Comorbidities on Survival of Patients with Myelofibrosis. *Cancers (Basel)* 2022; **14** [PMID: 35565461 DOI: 10.3390/cancers14092331]

37 **Accurso V**, Santoro M, Mancuso S, Contrino AD, Casimiro P, Sardo M, Raso S, Di Piazza F, Perez A, Bono M, Russo A, Siragusa S. Cardiovascular Risk in Essential Thrombocythemia and Polycythemia Vera: Thrombotic Risk and Survival. *Mediterr J Hematol Infect Dis* 2020; **12**: e2020008 [PMID: 31934318 DOI: 10.4084/MJHID.2020.008]

38 **Stein BL**, Rademaker A, Spivak JL, Moliterno AR. Gender and Vascular Complications in the JAK2 V617F-Positive Myeloproliferative Neoplasms. *Thrombosis* 2011; **2011**: 874146 [PMID: 22084670 DOI: 10.1155/2011/874146]

39 **Gu W**, Zhang Y, Sun T, Ju M, Liu X, Xue F, Chen Y, Liu W, Li H, Wang W, Chi Y, Yang R, Fu R, Bai J, Zhang L. Prediction of thrombosis in polycythemia vera: Development and validation of a multiple factor-based prognostic score system. *Res Pract Thromb Haemost* 2023; **7**: 100132 [PMID: 37113987 DOI: 10.1016/j.rpth.2023.100132]

40 **Horvat I**, Boban A, Zadro R, Antolic MR, Serventi-Seiwerth R, Roncevic P, Radman I, Sertic D, Vodanovic M, Pulanic D, Basic-Kinda S, Durakovic N, Zupancic-Salek S, Vrhovac R, Aurer I, Nemet D, Labar B. Influence of Blood Count, Cardiovascular Risks, Inherited Thrombophilia, and JAK2 V617F Burden Allele on Type of Thrombosis in Patients With Philadelphia Chromosome Negative Myeloproliferative Neoplasms. *Clin Lymphoma Myeloma Leuk* 2019; **19**: 53-63 [PMID: 30301673 DOI: 10.1016/j.clml.2018.08.020]

41 **Furuya C**, Hashimoto Y, Morishita S, Inano T, Ochiai T, Shirane S, Edahiro Y, Araki M, Ando M, Komatsu N. Reevaluation of cardiovascular risk factors for thrombotic events in 580 Japanese patients with essential thrombocythemia. *J Thromb Thrombolysis* 2023; **55**: 263-272 [PMID: 36484956 DOI: 10.1007/s11239-022-02751-0]

42 **Košťál M**, Schwarz J, Ovesná P, Penka M, Dulíček P; for CZEMP-Czech Group for Ph- Myeloproliferative neoplasms. Ph(-) myeloproliferative neoplasms and the related risk factors for stroke occurrence: Results from a registry of patients treated with Anagrelide. *J Thromb Thrombolysis* 2021; **51**: 112-119 [PMID: 32578055 DOI: 10.1007/s11239-020-02175-8]

43 **Barbui T**, Finazzi G, Falanga A. Myeloproliferative neoplasms and thrombosis. *Blood* 2013; **122**: 2176-2184 [PMID: 23823316 DOI: 10.1182/blood-2013-03-460154]

44 **Marchioli R**, Finazzi G, Landolfi R, Kutti J, Gisslinger H, Patrono C, Marilus R, Villegas A, Tognoni G, Barbui T. Vascular and neoplastic risk in a large cohort of patients with polycythemia vera. *J Clin Oncol* 2005; **23**: 2224-2232 [PMID: 15710945 DOI: 10.1200/JCO.2005.07.062]

45 **Hashimoto Y**, Ito T, Gotoh A, Nakamae M, Kimura F, Koike M, Kirito K, Wada H, Usuki K, Tanaka T, Mori T, Wakita S, Saito TI, Kada A, Saito AM, Shimoda K, Sugimoto Y, Kurokawa T, Tomita A, Edahiro Y, Akashi K, Matsumura I, Takenaka K, Komatsu N. Clinical

characteristics, prognostic factors, and outcomes of patients with essential thrombocythemia in Japan: the JSH-MPN-R18 study. *Int J Hematol* 2022; **115**: 208-221 [PMID: 34727329 DOI: 10.1007/s12185-021-03253-0]

46 **Chen J**, Dong H, Fu R, Liu X, Xue F, Liu W, Chen Y, Sun T, Ju M, Dai X, Li H, Wang W, Chi Y, Yang R, Zhang L. Machine learning analyses constructed a novel model to predict recurrent thrombosis in adults with essential thrombocythemia. *J Thromb Thrombolysis* 2023; **56**: 291-300 [PMID: 37249742 DOI: 10.1007/s11239-023-02833-7]

47 **Benevolo G**, Elli EM, Bartoletti D, Latagliata R, Tiribelli M, Heidel FH, Cavazzini F, Bonifacio M, Crugnola M, Binotto G, D'Addio A, Tieghi A, Bergamaschi M, Caocci G, Polverelli N, Bossi E, Auteri G, Carmosino I, Catani L, Cuneo A, Krampera M, Lanza F, Lemoli RM, Vianelli N, Breccia M, Palumbo GA, Cavo M, Palandri F. Impact of comorbidities and body mass index on the outcome of polycythemia vera patients. *Hematol Oncol* 2021; **39**: 409-418 [PMID: 33590502 DOI: 10.1002/hon.2843]

48 **Christensen SF**, Scherber RM, Brochmann N, Goros M, Gelfond J, Andersen CL, Flachs EM, Mesa R. Body Mass Index and Total Symptom Burden in Myeloproliferative Neoplasms Discovery of a U-shaped Association. *Cancers (Basel)* 2020; **12** [PMID: 32781663 DOI: 10.3390/cancers12082202]

49 **Aswad MH**, Kissova J, Ovesna P, Penka M. Risk factors of thrombosis in a cohort of 206 patients with BCR-ABL1 negative myeloproliferative neoplasms. *Neoplasma* 2021; **68**: 1341-1350 [PMID: 34704452 DOI: 10.4149/neo_2021_210729N1068]

50 **Grundy SM**. Hypertriglyceridemia, atherogenic dyslipidemia, and the metabolic syndrome. *Am J Cardiol* 1998; **81**: 18B-25B [PMID: 9526809 DOI: 10.1016/s0002-9149(98)00033-2]

51 **Manan MR**, Kipkorir V, Nawaz I, Waithaka MW, Srichawla BS, Găman AM, Diaconu CC, Găman MA. Acute myocardial infarction in myeloproliferative neoplasms. *World J Cardiol* 2023; **15**: 571-581 [PMID: 38058401 DOI: 10.4330/wjc.v15.i11.571]

52 **Mach F**, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, Chapman MJ, De Backer GG, Delgado V, Ference BA, Graham IM, Halliday A, Landmesser U, Mihaylova B, Pedersen TR, Riccardi G, Richter DJ, Sabatine MS, Taskinen MR, Tokgozoglu L, Wiklund O; ESC Scientific Document Group. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Eur Heart J* 2020; **41**: 111-188 [PMID: 31504418 DOI: 10.1093/eurheartj/ehz455]

53 **Grundy SM**. Metabolic syndrome update. *Trends Cardiovasc Med* 2016; **26**: 364-373 [PMID: 26654259 DOI: 10.1016/j.tcm.2015.10.004]

54 **American Diabetes Association**. 3. Prevention or Delay of Type 2 Diabetes: Standards of Medical Care in Diabetes-2021. *Diabetes Care* 2021; **44**: S34-S39 [PMID: 33298414 DOI: 10.2337/dc21-S003]

55 **Ge D**, Gooljar SB, Kyriakou T, Collins LJ, Swaminathan R, Snieder H, Spector TD, O'Dell SD. Association of common JAK2 variants with body fat, insulin sensitivity and lipid profile. *Obesity (Silver Spring)* 2008; **16**: 492-496 [PMID: 18239666 DOI: 10.1038/oby.2007.79]

56 **Rao TN**, Hansen N, Hilfiker J, Rai S, Majewska JM, Leković D, Gezer D, Andina N, Galli S, Cassel T, Geier F, Delezie J, Nienhold R, Hao-Shen H, Beisel C, Di Palma S, Dimeloe S, Trebicka J, Wolf D, Gassmann M, Fan TW, Lane AN, Handschin C, Dirnhofer S, Kröger N, Hess C, Radimerski T, Koschmieder S, Čokić VP, Skoda RC. JAK2-mutant hematopoietic cells display metabolic alterations that can be targeted to treat myeloproliferative neoplasms. *Blood* 2019; **134**: 1832-1846 [PMID: 31511238 DOI: 10.1182/blood.2019000162]

57 **Kleppe M**, Kwak M, Koppikar P, Riester M, Keller M, Bastian L, Hricik T, Bhagwat N, McKenney AS, Papalexi E, Abdel-Wahab O, Rampal R, Marubayashi S, Chen JJ, Romanet V, Fridman JS, Bromberg J, Teruya-Feldstein J, Murakami M, Radimerski T, Michor F, Fan R, Levine RL. JAK-STAT pathway activation in malignant and nonmalignant cells contributes to MPN pathogenesis and therapeutic response. *Cancer Discov* 2015; **5**: 316-331 [PMID: 25572172 DOI: 10.1158/2159-8290.CD-14-0736]

58 **Sharma V**, Wright KL, Epling-Burnette PK, Reuther GW. Metabolic Vulnerabilities and Epigenetic Dysregulation in Myeloproliferative Neoplasms. *Front Immunol* 2020; **11**: 604142 [PMID: 33329600 DOI: 10.3389/fimmu.2020.604142]

59 **Dalamaga M**, Christodoulatos GS. Adiponectin as a biomarker linking obesity and adiposopathy to hematologic malignancies. *Horm Mol Biol Clin Investig* 2015; **23**: 5-20 [PMID: 26057219 DOI: 10.1515/hmbci-2015-0016]

60 **Repsold L**, Joubert AM. Platelet Function, Role in Thrombosis, Inflammation, and Consequences in Chronic Myeloproliferative Disorders. *Cells* 2021; **10** [PMID: 34831257 DOI: 10.3390/cells10113034]

61 **Shoelson SE**, Lee J, Goldfine AB. Inflammation and insulin resistance. *J Clin Invest* 2006; **116**: 1793-1801 [PMID: 16823477 DOI: 10.1172/JCI29069]

62 **Mollé N**, Krichevsky S, Kermani P, Silver RT, Ritchie E, Scandura JM. Ruxolitinib can cause weight gain by blocking leptin signaling in the brain *via* JAK2/STAT3. *Blood* 2020; **135**: 1062-1066 [PMID: 32047890 DOI: 10.1182/blood.2019003050]

63 **Mesa RA**, Verstovsek S, Gupta V, Mascarenhas JO, Atallah E, Burn T, Sun W, Sandor V, Gotlib J. Effects of ruxolitinib treatment on metabolic and nutritional parameters in patients with myelofibrosis from COMFORT-I. *Clin Lymphoma Myeloma Leuk* 2015; **15**: 214-221.e1 [PMID: 25682576 DOI: 10.1016/j.clml.2014.12.008]

64 **Sapre M**, Tremblay D, Wilck E, James A, Leiter A, Coltoff A, Koshy AG, Kremyanskaya M, Hoffman R, Mascarenhas JO, Gallagher EJ. Metabolic Effects of JAK1/2 Inhibition in Patients with Myeloproliferative Neoplasms. *Sci Rep* 2019; **9**: 16609 [PMID: 31719581 DOI: 10.1038/s41598-019-53056-x]

65 **Podoltsev N**, Zhu M, Wang R, Zeidan AM, Wang X, Huntington SF, Giri S, Davidoff AJ, Gore SD, Ma X. Use of Statins, Survival and Incidence of Thrombosis Among Older Adults with Essential Thrombocythemia: A Population-Based Study. *Blood* 2018; **132**: 4865-4865 [DOI: 10.1182/blood-2018-99-119118]

66 **Tuyet Kristensen D**, Kisbye Øvlisen A, Hjort Kyneb Jakobsen L, Tang Severinsen M, Hannig LH, Starklint J, Hagemann Hilsøe M, Pommer Vallentin A, Brabrand M, Hasselbalch HC, El-Galaly TC, Stidsholt Roug A. Use of statins and risk of myeloproliferative neoplasms: a Danish nationwide case-control study. *Blood Adv* 2023; **7**: 3450-3457 [PMID: 36877642 DOI: 10.1182/bloodadvances.2023009784]

67 **Simpson-Poirier K**, Harnois M, Olney HJ, Sirhan S, Gratton MO, Assouline S, Laneuville P, Delage R, Mollica L, Busque L, Szuber N. Risk of infection in MPN patients in the era of Covid-19: A prospective multicenter study of 257 patients from the CML-MPN Quebec Research Group. *Am J Hematol* 2021; **96**: E200-E203 [PMID: 33719144 DOI: 10.1002/ajh.26159]

68 **Gao H**, Wang H, Shan G, Liu R, Chen H, Sun S, Liu Y. Prevalence of dyslipidemia and associated risk factors among adult residents of Shenmu City, China. *PLoS One* 2021; **16**: e0250573 [PMID: 33961634 DOI: 10.1371/journal.pone.0250573]

69 **Sung KC**, Huh JH, Ryu S, Lee JY, Scorletti E, Byrne CD, Kim JY, Hyun DS, Ko SB. Low Levels of Low-Density Lipoprotein Cholesterol and Mortality Outcomes in Non-Statin Users. *J Clin Med* 2019; **8** [PMID: 31581520 DOI: 10.3390/jcm8101571]

70 **Sun Y**, Cai Y, Cen J, Zhu M, Pan J, Wang Q, Wu D, Chen S. Pegylated Interferon Alpha-2b in Patients With Polycythemia Vera and Essential Thrombocythemia in the Real World. *Front Oncol* 2021; **11**: 797825 [PMID: 34993148 DOI: 10.3389/fonc.2021.797825]

71 **Chen L**, Deng H, Cui H, Fang J, Zuo Z, Deng J, Li Y, Wang X, Zhao L. Inflammatory responses and inflammation-associated diseases in organs. *Oncotarget* 2018; **9**: 7204-7218 [PMID: 29467962 DOI: 10.18632/oncotarget.23208]

72 **Watson CJ**, Papula AL, Poon GYP, Wong WH, Young AL, Druley TE, Fisher DS, Blundell JR. The evolutionary dynamics and fitness landscape of clonal hematopoiesis. *Science* 2020; **367**: 1449-1454 [PMID: 32217721 DOI: 10.1126/science.aay9333]

73 **Marnell CS**, Bick A, Natarajan P. Clonal hematopoiesis of indeterminate potential (CHIP): Linking somatic mutations, hematopoiesis, chronic inflammation and cardiovascular disease. *J Mol Cell Cardiol* 2021; **161**: 98-105 [PMID: 34298011 DOI: 10.1016/j.yjmcc.2021.07.004]

74 **Rodríguez-Rodero S**, Fernández-Morera JL, Menéndez-Torre E, Calvanese V, Fernández AF, Fraga MF. Aging genetics and aging. *Aging Dis* 2011; **2**: 186-195 [PMID: 22396873]

75 **Blackburn EH**, Greider CW, Szostak JW. Telomeres and telomerase: the path from maize, Tetrahymena and yeast to human cancer and aging. *Nat Med* 2006; **12**: 1133-1138 [PMID: 17024208 DOI: 10.1038/nm1006-1133]

76 **Greenwood MJ**, Lansdorp PM. Telomeres, telomerase, and hematopoietic stem cell biology. *Arch Med Res* 2003; **34**: 489-495 [PMID: 14734088 DOI: 10.1016/j.arcmed.2003.07.003]

77 **Salpea KD**, Talmud PJ, Cooper JA, Maubaret CG, Stephens JW, Abelak K, Humphries SE. Association of telomere length with type 2 diabetes, oxidative stress and UCP2 gene variation. *Atherosclerosis* 2010; **209**: 42-50 [PMID: 19889414 DOI: 10.1016/j.atherosclerosis.2009.09.070]

78 **von Zglinicki T**. Oxidative stress shortens telomeres. *Trends Biochem Sci* 2002; **27**: 339-344 [PMID: 12114022 DOI: 10.1016/s0968-0004(02)02110-2]

79 **Tomás-Loba A**, Flores I, Fernández-Marcos PJ, Cayuela ML, Maraver A, Tejera A, Borrás C, Matheu A, Klatt P, Flores JM, Viña J, Serrano M, Blasco MA. Telomerase reverse transcriptase delays aging in cancer-resistant mice. *Cell* 2008; **135**: 609-622 [PMID: 19013273 DOI: 10.1016/j.cell.2008.09.034]

80 **Miles B**, Tadi P. Genetics, Somatic Mutation. 2023 Apr 17. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan- [PMID: 32491819]

81 **Liguori I**, Russo G, Curcio F, Bulli G, Aran L, Della-Morte D, Gargiulo G, Testa G, Cacciatore F, Bonaduce D, Abete P. Oxidative stress, aging, and diseases. *Clin Interv Aging* 2018; **13**: 757-772 [PMID: 29731617 DOI: 10.2147/CIA.S158513]

82 **Salisbury D**, Bronas U. Reactive oxygen and nitrogen species: impact on endothelial dysfunction. *Nurs Res* 2015; **64**: 53-66 [PMID: 25502061 DOI: 10.1097/NNR.0000000000000068]

83 **Mayerhofer E**, Strecker C, Becker H, Georgakis MK, Uddin MM, Hoffmann MM, Nadarajah N, Meggendorfer M, Haferlach T, Rosand J, Natarajan P, Anderson CD, Harloff A, Hoermann G. Prevalence and Therapeutic Implications of Clonal Hematopoiesis of Indeterminate Potential in Young Patients With Stroke. *Stroke* 2023; **54**: 938-946 [PMID: 36789775 DOI: 10.1161/STROKEAHA.122.041416]

84 **Kuznetsova PI**, Raskurazhev AA, Konovalov RN, Krotenkova MV, Chechetkin AO, Lagoda OV, Melikhyan AL, Tanashyan MM. Covert Brain Infarcts in Patients with Philadelphia Chromosome-Negative Myeloproliferative Disorders. *J Clin Med* 2021; **11** [PMID: 35011753 DOI: 10.3390/jcm11010013]

85 **Xiang Q**, Tian F, Xu J, Du X, Zhang S, Liu L. New insight into dyslipidemia-induced cellular senescence in atherosclerosis. *Biol Rev Camb Philos Soc* 2022; **97**: 1844-1867 [PMID: 35569818 DOI: 10.1111/brv.12866]

86 **Hasselbalch HC**. Perspectives on chronic inflammation in essential thrombocythemia, polycythemia vera, and myelofibrosis: is chronic inflammation a trigger and driver of clonal evolution and development of accelerated atherosclerosis and second cancer? *Blood* 2012; **119**: 3219-3225 [PMID: 22318201 DOI: 10.1182/blood-2011-11-394775]

87 **Baldini C**, Moriconi FR, Galimberti S, Libby P, De Caterina R. The JAK-STAT pathway: an emerging target for cardiovascular disease in rheumatoid arthritis and myeloproliferative neoplasms. *Eur Heart J* 2021; **42**: 4389-4400 [PMID: 34343257 DOI: 10.1093/eurheartj/ehab447]

88 **Liu W**, Östberg N, Yalcinkaya M, Dou H, Endo-Umeda K, Tang Y, Hou X, Xiao T, Fidler TP, Abramowicz S, Yang YG, Soehnlein O, Tall AR, Wang N. Erythroid lineage Jak2V617F expression promotes atherosclerosis through erythrophagocytosis and macrophage ferroptosis. *J Clin Invest* 2022; **132** [PMID: 35587375 DOI: 10.1172/JCI155724]

89 **Wang W**, Liu W, Fidler T, Wang Y, Tang Y, Woods B, Welch C, Cai B, Silvestre-Roig C, Ai D, Yang YG, Hidalgo A, Soehnlein O, Tabas I, Levine RL, Tall AR, Wang N. Macrophage Inflammation, Erythrophagocytosis, and Accelerated Atherosclerosis in Jak2 (V617F) Mice. *Circ Res* 2018; **123**: e35-e47 [PMID: 30571460 DOI: 10.1161/CIRCRESAHA.118.313283]

90 **Poisson J**, Tanguy M, Davy H, Camara F, El Mdawar MB, Kheloufi M, Dagher T, Devue C, Lasselin J, Plessier A, Merchant S, Blanc-Brude O, Souyri M, Mougenot N, Dingli F, Loew D, Hatem SN, James C, Villeval JL, Boulanger CM, Rautou PE. Erythrocyte-derived microvesicles induce arterial spasms in JAK2V617F myeloproliferative neoplasm. *J Clin Invest* 2020; **130**: 2630-2643 [PMID: 32045382 DOI: 10.1172/JCI124566]

91 **Majeti R**, Jamieson C, Pang WW, Jaiswal S, Leeper NJ, Wernig G, Weissman IL. Clonal Expansion of Stem/Progenitor Cells in Cancer, Fibrotic Diseases, and Atherosclerosis, and CD47 Protection of Pathogenic Cells. *Annu Rev Med* 2022; **73**: 307-320 [PMID: 35084991 DOI: 10.1146/annurev-med-042420-104436]

92 **Yvan-Charvet L**, Pagler T, Gautier EL, Avagyan S, Siry RL, Han S, Welch CL, Wang N, Randolph GJ, Snoeck HW, Tall AR. ATP-binding cassette transporters and HDL suppress hematopoietic stem cell proliferation. *Science* 2010; **328**: 1689-1693 [PMID: 20488992 DOI: 10.1126/science.1189731]

93 **Tang Y**, Liu W, Wang W, Fidler T, Woods B, Levine RL, Tall AR, Wang N. Inhibition of JAK2 Suppresses Myelopoiesis and Atherosclerosis in Apoe(-/-) Mice. *Cardiovasc Drugs Ther* 2020; **34**: 145-152 [PMID: 32086626 DOI: 10.1007/s10557-020-06943-9]

94 **Skov V**, Thomassen M, Kjaer L, Larsen MK, Knudsen TA, Ellervik C, Kruse TA, Hasselbalch HC. Whole blood transcriptional profiling reveals highly deregulated atherosclerosis genes in Philadelphia-chromosome negative myeloproliferative neoplasms. *Eur J Haematol* 2023; **111**: 805-814 [PMID: 37640394 DOI: 10.1111/ejh.14081]

95 **Solli CN**, Chamat-Hedemand S, Elming H, Ngo A, Kjaer L, Skov V, Sørensen AL, Ellervik C, Hasselbalch H, Bruun NE. High JAK2V617F variant allele frequency is associated with coronary artery but not aortic valve calcifications in patients with Philadelphia-negative myeloproliferative neoplasms. *Eur J Haematol* 2023; **111**: 400-406 [PMID: 37286366 DOI: 10.1111/ejh.14019]

96 **Kwon SS**, Yoon SY, Jeong SY, Lee MY, Kim KH, Lee N, Won JH. Neutrophil-lymphocyte ratio and carotid plaque burden in patients with essential thrombocythemia and polycythemia vera. *Nutr Metab Cardiovasc Dis* 2022; **32**: 1913-1916 [PMID: 35606226 DOI: 10.1016/j.numecd.2022.04.013]

97 **Anžič Drofenik A**, Vrtovec M, Božič Mijovski M, Sever M, Preložnik Zupan I, Kejžar N, Blinc A. Progression of coronary calcium burden and carotid stiffness in patients with essential thrombocythemia associated with JAK2 V617F mutation. *Atherosclerosis* 2020; **296**: 25-31 [PMID: 32005002 DOI: 10.1016/j.atherosclerosis.2020.01.001]

98 **Jalkanen J**, Hollmén M, Maksimow M, Jalkanen S, Hakovirta H. Serum cytokine levels differ according to major cardiovascular risk factors in patients with lower limb atherosclerosis. *Cytokine* 2019; **114**: 74-80 [PMID: 30442459 DOI: 10.1016/j.cyto.2018.11.001]

99 **Herbreteau L**, Couturaud F, Hoffmann C, Bressollette L, Pan-Petesch B, Rio L, Lippert E, Ianotto JC. Atrial fibrillation and peripheral arterial disease define MPN patients with very high risk of thrombosis. *Thromb Res* 2023; **226**: 93-99 [PMID: 37141796 DOI: 10.1016/j.thromres.2023.04.021]

100 **Gaman AM**, Moisa C, Diaconu CC, Gaman MA. Crosstalk between Oxidative Stress, Chronic Inflammation and Disease Progression in Essential Thrombocythemia. *Rev Chim* 2019; **70**: 3486-3489 [DOI: 10.37358/RC.19.10.7581]

World Journal of Clinical Oncology

Submit a Manuscript: https://www.f6publishing.com

World J Clin Oncol 2024 June 24; 15(6): 730-744

DOI: 10.5306/wjco.v15.i6.730

ISSN 2218-4333 (online)

REVIEW

Systemic oncological therapy in breast cancer patients on dialysis

Salman Khan, Ghada Araji, Ekrem Yetiskul, Praneeth Reddy Keesari, Fadi Haddadin, Zaid Khamis, Varun Chowdhry, Muhammad Niazi, Sarah Afif, Meekoo Dhar, Suzanne El-Sayegh

Specialty type: Oncology

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification

Scientific Quality: Grade A
Novelty: Grade A
Creativity or Innovation: Grade A
Scientific Significance: Grade A

P-Reviewer: Wang Z, China

Received: March 24, 2024
Revised: May 12, 2024
Accepted: May 29, 2024
Published online: June 24, 2024
Processing time: 91 Days and 8.7 Hours

Salman Khan, Ghada Araji, Ekrem Yetiskul, Praneeth Reddy Keesari, Fadi Haddadin, Zaid Khamis, Varun Chowdhry, Suzanne El-Sayegh, Department of Internal Medicine, Northwell Health - Staten Island University Hospital, Staten Island, NY 10305, United States

Muhammad Niazi, Meekoo Dhar, Department of Hematology and Oncology, Northwell Health - Staten Island University Hospital, Staten Island, NY 10305, United States

Sarah Afif, Department of Internal Medicine, CUNY School of Medicine, New York, NY 10031, United States

Corresponding author: Salman Khan, MD, Academic Fellow, Academic Research, Department of Internal Medicine, Northwell Health - Staten Island University Hospital, 475 Seaview Ave, Staten Island, NY 10305, United States. skhan114@northwell.edu

Abstract

The advancement of renal replacement therapy has significantly enhanced the survival rates of patients with end-stage renal disease (ESRD) over time. However, this prolonged survival has also been associated with a higher likelihood of cancer diagnoses among these patients including breast cancer. Breast cancer treatment typically involves surgery, radiation, and systemic therapies, with approaches tailored to cancer type, stage, and patient preferences. However, renal replacement therapy complicates systemic therapy due to altered drug clearance and the necessity for dialysis sessions. This review emphasizes the need for optimized dosing and administration strategies for systemic breast cancer treatments in dialysis patients, aiming to ensure both efficacy and safety. Additionally, challenges in breast cancer screening and diagnosis in this population, including soft-tissue calcifications, are highlighted.

Key Words: Breast cancer; Systemic therapy; Renal replacement therapy; Dialysis; End-stage renal disease; Hormone therapy; Chemotherapy

Core Tip: Optimizing systemic breast cancer therapy in dialysis patients requires tailored approaches due to altered drug clearance and dialysis sessions' necessity. This review emphasizes the significance of optimizing dosing and administration strategies, ensuring both efficacy and safety. Challenges in breast cancer screening, including soft-tissue calcifications, are highlighted, underlining the necessity for precise diagnostic strategies in this population. Furthermore, nuanced understanding and guidelines are imperative to navigate the complexity of oncological treatment in dialysis patients, ultimately enhancing patient outcomes.

Citation: Khan S, Araji G, Yetiskul E, Keesari PR, Haddadin F, Khamis Z, Chowdhry V, Niazi M, Afif S, Dhar M, El-Sayegh S. Systemic oncological therapy in breast cancer patients on dialysis. *World J Clin Oncol* 2024; 15(6): 730-744
URL: https://www.wjgnet.com/2218-4333/full/v15/i6/730.htm
DOI: https://dx.doi.org/10.5306/wjco.v15.i6.730

INTRODUCTION

The number of patients with end-stage renal disease (ESRD) worldwide has increased rapidly over the past few decades. With the development of renal replacement therapy, patients with ESRD have had improved survival with time[1], which increased their likelihood of being diagnosed with various cancers over time and increased the incidence of various malignancies in this population[2-5]. In a study conducted in northeastern Italy, the risk of developing *de novo* malignancies was 1.3 times greater in the dialysis group than in the general population. This increased risk was particularly notable for certain types of cancer, including nonmelanoma skin cancer, kidney cancer, oral cavity cancer, and Kaposi's sarcoma[6].

Breast cancer is the most common cancer worldwide[7]. Some studies have shown an increased risk of breast cancer in dialysis patients[8]. According to the United States Renal Data System, in the years 1996-2009, 3552 women on hemodialysis (HD) were diagnosed with breast cancer, which is 42% higher incidence than in the general population[5]. A prospective cohort study with a median follow-up time of 12.8 years explored cancer mortality instead of incidence. Compared with participants with an estimated glomerular filtration rate (eGFR) > 60 mL/min/1.73 m^2, the hazard ratio (HR) for breast cancer death for women with an eGFR < 60 mL/min/1.73 m^2 was 1.99 (95% confidence interval: 1.05- 3.85; P = 0.01) after adjusting for age, smoking status, and employment status. This increase in mortality was attributed to a few different reasons. First, patients with ESRD often have multiple other medical comorbidities, the management of which can lead to route cancer screening not being a priority. Second, adjusting the dose of cytotoxic agents for patients with reduced kidney function can be challenging, and therefore, treatment can be suboptimal. Third, patients with ESRD may have more aggressive breast cancer, given the state of chronic inflammation induced by continuous exposure to oxidative stress (leading to tumor proliferation) and uremia (accentuating mitogenesis)[9]. Although ESRD has not been proven to be a risk factor for breast cancer, it has a significant impact on its therapy because it drastically changes the pharmacokinetics of cytotoxic drugs and other systemic agents used in breast cancer treatment.

Surgery, radiation, and systemic therapies are the mainstay of the treatment of breast cancer. The specific treatment approach is usually tailored based on the type and stage of cancer, the patient's health status, and personal treatment preferences. Surgical intervention in breast cancer management is primarily focused on the excision of malignant tissue, and it can be preceded or followed by chemotherapy, radiation therapy, or both. Radiation therapy employs potent energy beams to destroy or inhibit cancer cell growth and encompasses external and internal radiation therapy[10]. Systemic therapies are designed to target cancer cells throughout the body and can be administered as adjuvant, neoadjuvant, or palliative treatment. The primary categories include chemotherapy, hormone therapy [used in estrogen and progesterone receptor (PR)-positive cancers], anti-human epidermal growth factor receptor 2 (HER2) therapy, cyclin-dependent kinase 4/6 (CDK4/6) inhibitors, poly ADP-ribose polymerase (PARP) inhibitors, and immunotherapy[11,12]. When treating breast cancer patients with ESRD, renal replacement therapy does not limit the utility of surgical treatment and radiotherapy; however, it significantly impacts systemic therapies due to the reduction or loss of renal clearance of drugs and their metabolites and their elimination during dialysis sessions. This alteration of pharmacokinetics significantly affects the dosage and timing of administration of these drugs in dialysis patients.

The purpose of this review is to highlight current knowledge on systemic treatments used in the adjuvant, neoadjuvant, and palliative treatment of breast cancer in dialysis patients. It highlights the existing research on recommended dose modifications and timing of these medications' administration about dialysis in this specific group of patients to guarantee the most effective and safe treatment of breast cancer. It also sheds light on the challenges faced in breast cancer screening and diagnosis in this population due to soft-tissue calcifications.

IMPLICATIONS OF SOFT-TISSUE CALCIFICATIONS IN ESRD ON BREAST CANCER SCREENING

Patients with chronic kidney disease (CKD) and ESRD are known to develop soft-tissue calcifications in multiple tissues, including the breast, mainly secondary to hyperparathyroidism[13-15]. This can pose challenges in breast cancer screening in this population. They often develop vascular calcifications, which may be dense areas on mammograms and mimic the appearance of breast microcalcifications, making distinguishing between benign and malignant findings

difficult. This may lead to false positive or false negative findings in breast cancer screening in this population. False positives can result in unnecessary workups and interventions, while false negatives may lead to delayed diagnosis and treatment[16-18]. The investigation of this issue is critical in order to provide high-quality, precise breast care to women with CKD or ESRD, yet there is currently little evidence available.

Studies have shown that breast vascular calcifications increase with the progression of CKD[19]. However, data on the morphological characteristics of breast calcifications in this population, the incidence of benign *vs* malignant calcifications, and their clinical implication are limited. Castellanos *et al*[20] reviewed the mammograms, traced the recommended workup of women on HD, and compared it to that of women with normal renal function. The incidence of calcifications was higher in HD patients but was attributed mainly to benign calcification patterns. Vascular calcification was the most common pattern in both groups when comparing the categories of benign calcifications. At the same time, HD patients were likelier to have other calcification patterns, including parenchymal spherical and lucent calcification patterns. However, even when comparing the incidence of calcifications commonly considered to be associated with malignancy (BI-RADS 4 and 5) prompting biopsy, patients on HD had significantly higher incidence and a greater probability of being recommended for biopsy.

Further studies with a large sample size are recommended to investigate the incidence, morphologic characteristics, and clinical implications of breast calcifications in HD patients to direct screening and biopsy recommendations in this population. At this time, mammography remains the gold standard for screening breast cancer in women on dialysis. Clinicians managing these patients should be aware of the increased incidence of calcifications and the risk for further workup and interventions in these patients.

SYSTEMIC THERAPIES

In the context of treating breast cancer in patients with ESRD on HD, the selection and administration of chemotherapeutic agents are marked by a significant degree of complexity and confusion. This stems mainly from the altered pharmacokinetics in these patients, necessitating careful consideration of drug metabolism and renal clearance. The decision-making process is further complicated by the need for potential dose adjustments and the impact of renal function on drug efficacy and toxicity. While hormone therapies and other systemic treatments offer additional options, their use in the ESRD population also requires a nuanced understanding of their interaction with renal dysfunction. The current scenario highlights a critical need for more comprehensive research and precise guidelines to navigate the intricacies of oncological treatment in this unique patient group. This would enable healthcare providers to optimize therapy, balancing efficacy and safety and ultimately improving patient outcomes in breast cancer patients undergoing HD.

Hormone therapies

Approximately 20%-30% of breast cancers express hormone receptors, including estrogen receptors (ERs) and PRs. Hormone receptor-positive breast cancers depend on these hormones for growth and spread. Various hormone therapy agents are used to treat these hormone receptor-positive breast cancers. However, prescribing these agents for dialysis patients is unique because of alterations in drug metabolism and the high pill burden often associated with dialysis.

Tamoxifen

Tamoxifen is a selective ER modulator that works by inhibiting estrogen's action on breast cancer cells. It is often used for premenopausal women or those with contraindications to aromatase inhibitors (AIs). The CYP2D6 and CYP3A4 enzymes metabolize tamoxifen into more potent metabolites[21]. The drug avidly binds (95%) to proteins and has high lipophilicity. It is metabolized by cytochrome P450 enzymes in the liver, forming 4-hydroxy tamoxifen and N-desmethyltamoxifen. Approximately 60 % of the drug is excreted unaltered in feces and 9%-14% in the urine. The plasma level of tamoxifen remains constant for 3-4 weeks when it is daily dosed at 20-40 mg once a day. It is noted that the half-life of the drug is 5-7 days, while the metabolite N-desmethyl tamoxifen needs 13 days to be cleared from the body[22]. The study by Langenegger *et al*[23] described that the use of tamoxifen in an HD does not need any dose adjustments. The plasma concentration of the drug was similar in HD patients compared to non-HD patients. It is advisable that due to the drug's high lipophilicity, it should be administered before the HD session. However, concomitant medications used in dialysis may inhibit these enzyme systems, leading to reduced efficacy of tamoxifen. Close monitoring is required if this approach is used in dialysis patients.

AIs

This group of drugs includes anastrozole, letrozole, and exemestane. These drugs work by suppressing estrogen production and achieving the estrogen deprivation state in a postmenopausal woman. AIs are preferred over tamoxifen for treating postmenopausal women with hormone receptor-positive breast cancer[24].

Anastrozole is a common drug for breast cancer in early and metastatic cancer stages. It is 40% bound to plasma proteins. The liver is responsible for 85% of its metabolism and excretes into feces, but only 11% of the total drug is excreted by the kidneys. The study by Langenegger *et al*[23] mentioned that the half-life of the drug is 41 hours. According to the same study, the serum concentration of anastrozole in patients on HD is similar to those seen in patients with normal renal function. Therefore, it does not need any dose adjustment in patients with HD. However, due to low molecular mass and strong affinity for plasma proteins, it is advisable to take the drug after an HD session.

Exemestane avidly binds to proteins (90%) and is inactivated by the liver, which means the metabolites are not biologically active. It is noted that only a small portion of the drug, which accounts for 1%, is excreted unaltered in the urine. For individuals with creatinine clearance (CC) below 30 mL/min, the extent of exemestane absorption, shown by the area under the curve (AUC), is twice as much as that in individuals with normal kidney function. There are no specific guidelines on the administration and safety of this medication for patients with a GFR below 30 mL/min/1.73 m^2, including patients on renal replacement therapies. Therefore, dose adjustments for patients with CKD are not recommended, but extreme caution is advised when administering the drug to patients undergoing dialysis. It is preferable to avoid the drug and use other alternative options if available; otherwise, exemestane should be used as a last resort in that scenario[25].

Similarly, letrozole, an AI, is changed into its inactive metabolite (carbinol) in the liver by (isoenzymes: 3A4, 2A6 of cytochrome P450)[23]. The characteristics of the drug show that it does not need any dose adjustment for patients with CKD and CC greater than 30 mL/min. There is no data on patients with CC < 30 mL/min. There is a single clinical report on a patient treated with Letrozole and lapatinib for breast cancer on HD; the therapy was well tolerated without adjusting the dosage[26].

Fulvestrant

Fulvestrant is another ER-directed agent that works differently from tamoxifen or AIs. It is a selective ER down regulator with no agonist effects. It is highly bound to plasma lipoproteins (99%), is metabolized very slowly in the liver *via* the same pathways as endogenous steroids, and is excreted into feces[27]. Although CYP3A4 metabolizes fulvestrant, pharmacokinetic studies have shown that dialysis patients may not require dose adjustments. The biological half-life of the drug is estimated to be 40 days. No data on the drug's safety and pharmacokinetics in dialysis patients is available. Due to the limited role of the kidney in its elimination process, the drug can be used in ESRD patients on HD in unchanged doses. Hence, this approach may benefit patients unsuitable for other hormone therapies[28].

Megestrol acetate

Megestrol acetate is a synthetic progestin that has anticachectic as well as antineoplastic effects and is used in the treatment of advanced breast cancer with disease progression[29]. The drug has high affinity to bind albumins and there is limited role of the kidneys in its excretion process. The liver slowly metabolizes the drug, and its metabolites are excreted into feces. Megestrol acetate has been evaluated in numerous trials for its safety in dialysis patients and it can be used in the therapy of metastatic breast cancer in this population[30].

CDK 4/6 inhibitors

More recently, CDK 4/6 inhibitor drugs such as (palbociclib, ribociclib, and abemaciclib) have been introduced for hormone receptor-positive metastatic breast cancers. These agents enhance the efficacy of antiestrogen drugs. These drugs undergo significant hepatic metabolism *via* CYP3A enzymes. All the CKD 4/6 inhibitors are protein-bound molecules metabolized in the liver by cytochrome P450 isoenzymes and are excreted into feces. Although no studies are available yet, according to the drug's pharmacokinetics, there is no need to reduce the dose of the drug in CKD/ESRD patients on HD. On the contrary, these drugs may have some nephroprotective effects by inhibiting the CDK4/6 pathway and have been shown to decrease kidney injury caused by cisplatin[31]. It is essential to mention that in approximately 40% of the individuals, abemaciclib is associated with a reversible increase in serum creatinine concentration greater than 50% over the baseline levels[32]. The drug inhibited renal tubular secretion of creatinine without changes in the measured GFR and the structural markers of kidney tubular injury[33].

CHEMOTHERAPEUTIC AGENTS

Cyclophosphamide

Cyclophosphamide (CTX), a frequently utilized chemotherapeutic drug, affects various cell functions. Its therapeutic efficacy is contingent upon metabolic activation, predominantly in the liver. This activation is facilitated by P450 isoenzymes, which convert P450 into its active derivatives, phosphoramide mustard, which contributes to cancer-fighting capabilities, and acrolein, which is known for its toxicity and potential link to bladder cancer[34]. Notably, the ability of CTX to suppress immune functions, including reducing lymphocyte counts and inhibiting the activity of both T cells and B cells, accounts for its application in treating certain autoimmune disorders and preventing organ rejection in transplant recipients.

Approximately 50% to 70% of CTX is excreted by kidneys within 48 hours, with approximately 32% expelled in its unchanged form. The exploration of CTX in patients undergoing dialysis has been limited, yet some noteworthy examples exist in the literature. For example, a case study reported a 48-year-old woman with breast cancer who was receiving HD[35]. The study revealed that the peak plasma concentration of CTX was approximately 49 μg/mL and the *in vivo* half-life of the drug extended to 67 hours. Based on these findings, it is evident that CTX is dialyzable and, as such, should preferably be administered post-HD sessions or on days when dialysis is not scheduled. In another study, CTX was administered intravenously at a dose of 0.5-1 g/m^2 for 1 hour in HD patients; an HD session was done 7 hours after administration. Mean CTX clearance was moderately lower in HD patients than in patients with normal renal function. The AUC was increased in HD patients. Thus, it is necessary to reduce the dose of CTX by 25% in HD patients[36].

Two-drug regimen: AC/EC

Anthracyclines, particularly doxorubicin (doxorubicin; also known as adriamycin), function as antibiotics that interfere with DNA by disrupting topoisomerase-II activity and generating free radicals. These processes hinder DNA replication and transcription, ultimately leading to cellular death. A known side effect of doxorubicin is cardiotoxicity, necessitating regular monitoring through echocardiography for patients receiving this treatment.

The regimen is typically administered every two to three weeks over several cycles, and the frequency and duration of the anthracycline regimen, including doxorubicin, depends on multiple factors, such as the stage and specific type of breast cancer. Research on the pharmacokinetics of doxorubicin in patients with renal insufficiency is sparse, presenting challenges in understanding its efficacy and safety in this population. Both doxorubicin and its primary active metabolite doxorubicinol are cleared renally.

Its efficacy is enhanced by its ability to target cancer cells *via* diverse mechanisms, increasing potential side effects. For patients undergoing HD, there are specific guidelines for the anthracycline regimen, particularly for patients receiving doxorubicin. A reduction in the doxorubicin dose of 20%-25% is generally considered safe for patients with CKD/ESRD, including those receiving HD treatment. In dual-drug regimens for HD patients, administering these medications on nondialysis days is advised to ensure optimal treatment efficacy and safety[37].

Paclitaxel and docetaxel

Paclitaxel and docetaxel, which are part of the taxane family of chemotherapeutic drugs, are utilized in treating a variety of cancers, such as breast, ovarian, lung, and prostate cancer. Paclitaxel's mode of action involves stabilizing cellular microtubules, which are crucial for cell division, thereby inducing cell death, particularly in fast-dividing cancer cells[38]. A notable side effect of paclitaxel is peripheral neuropathy, characterized by numbness and pain. Additionally, it can cause neutropenia, hair loss, and hypersensitivity reactions, the latter often linked to its formulation. Both drugs strongly bind to proteins such as albumin and alpha-1-glycoprotein. These drugs are metabolized predominantly in the liver *via* the cytochrome P450 system, followed by excretion primarily into the bile and, to a lesser extent, in the urine[39].

Studies indicate that the pharmacokinetics of a standard dose of paclitaxel (135 mg/m^2 administered over three hours intravenously) in patients on HD mirrors those with normal renal function[40]. These findings suggested that renal function does not significantly impact the elimination of the drug. The typical dosage for breast cancer treatment with paclitaxel is 80 mg/m^2 administered weekly. Additionally, docetaxel has shown good tolerability in a 72-year-old patient with prostate cancer undergoing HD[41]. Furthermore, Watanabe *et al*[40] reported the safe and practical application of paclitaxel in a 40-year-old woman on HD.

Gemcitabine

Gemcitabine, a key chemotherapeutic drug, is crucial in the treatment of various solid tumors, including breast cancer. It functions as a deoxycytidine analog and disrupts DNA synthesis. This disruption occurs when gemcitabine integrates into DNA during the S phase of the cell cycle, leading to an interruption in the DNA chain. Metabolically, gemcitabine is transformed into active forms, namely, diphosphate and triphosphate nucleosides[42]. The diphosphate form is essential because it inhibits ribonucleotide reductase, an enzyme critical for synthesizing deoxyribonucleotides. Inhibiting this enzyme *via* gemcitabine leads to a reduced pool of deoxynucleotides, thus hindering DNA synthesis. This sequence of events triggers apoptosis in cancer cells. The drug's effectiveness is also augmented by a self-enhancing mechanism that increases its uptake into cells and integration into DNA, mainly by inhibiting ribonucleotide reductase.

Regarding metabolic processing, gemcitabine primarily undergoes processing in the liver, with limited renal involvement, as only a minor portion is bound to plasma proteins and undergoes renal filtration. In conjunction with HD, the kidneys facilitate the removal of the primary nontoxic metabolite difluorodeoxyuridine. Significantly, in patients with CKD and ESRD, administering gemcitabine at doses up to 1200 mg/m^2 did not differ in toxicity or pharmacokinetics compared to that in individuals with normal renal function, indicating that adjusting the dosage for CKD/ESRD patients on HD may not be essential[43].

Carboplatin

Carboplatin, a chemotherapeutic agent that is a platinum compound, is extensively utilized in treating numerous cancer types, including breast cancer. It resembles cisplatin but is differentiated by its unique toxicity profile. The primary anticancer action of carboplatin involves the formation of crosslinks within DNA, thereby disrupting both DNA replication and transcription processes, which is particularly effective against rapidly multiplying tumor cells. This agent's impact is not limited to a specific phase of the cell cycle, allowing it to affect cancer cells at various stages of growth. It is notably efficacious in the treatment of triple-negative breast cancer (TNBC), a subtype devoid of estrogen, progesterone, and HER2/neu receptors[44].

Carboplatin is administered intravenously and remains unbound mainly in the bloodstream initially but predominantly binds to proteins within 24 hours. Approximately 55%-70% of the drug is eliminated by the kidneys within the first 24 hours[44]. Carboplatin is considered safe for individuals with a CC above 20 mL/min, although dosage adjustments are required when the CC is less than 60 mL/min to avoid myelotoxicity[45]. In cases of renal impairment, the Calvert formula is typically used for dosage calculations, aiming for a specific AUC[46]. Although not standard practice, dialysis patients may receive reduced carboplatin doses. The AIOM guidelines recommend adjusting an AUC × 25 mg dosage for HD patients[37].

To ensure efficient removal, HD and peritoneal dialysis (PD) should be carried out within 12-18 h after carboplatin infusion before binding to proteins, decreasing dialysis. Research by Hiraike *et al*[47] showed that standard doses of carboplatin, as per the Calvert formula, maintain predictable pharmacokinetics if HD is initiated one hour after adminis-

tration. In PD patients, such as those undergoing continuous ambulatory PD, approximately 20% of carboplatin is removed *via* dialysate, and its half-life is extended compared to that of patients with normal kidney function[48]. Although ideally administered on dialysis days just before the session, current protocols often suggest giving carboplatin on non-dialysis days for logistical reasons[37].

Fluorouracil

5-fluorouracil (5-FU), a molecular entity weighing 130 Da, is a pyrimidine antimetabolite used in chemical treatment. The mechanism of action of 5-FU lies in its structural resemblance to uracil and thymidine, fundamental elements of RNA and DNA. It undergoes metabolic conversion into substances interrupting RNA and DNA synthesis[49]. A key metabolite, fluorodeoxyuridine monophosphate, inhibits explicitly thymidylate synthase, which is crucial for synthesizing the thymidine necessary for DNA replication. This inhibition results in a thymidine deficit, disrupting DNA synthesis and leading to the death of rapidly multiplying cancer cells. Simultaneously, the presence of 5-FU metabolites in RNA affects standard RNA processing. Despite its efficacy in cancer treatment, 5-FU has a range of side effects. Myelosuppression is frequently observed, which can lead to reduced blood cell counts and increased risks of infection, anemia, and bleeding. Gastrointestinal discomfort, such as nausea, diarrhea, and mucositis, are other common side effects. Cardiotoxicity, manifesting as chest pain or irregular heartbeats, and neurotoxic symptoms such as confusion or lack of coordination are also associated with 5-FU therapy.

Its half-life averages approximately 16 minutes when administered intravenously, although this can vary depending on the administered dose. Notably, a mere 15% of the administered 5-FU is eliminated *via* the urine in its original form. In the context of end-stage kidney disease (ESKD), the standard protocol involves administering 5-FU doses after HD sessions or on days without dialysis, considering the modified excretion patterns in such patients. Given these potential adverse effects, careful monitoring and dosage adjustments are imperative to ensure a safe balance between the drug's effectiveness and patient well-being, particularly in those with impaired renal function[50].

Capecitabine

Capecitabine, with a molecular weight of 359.3 Da, is a precursor to 5-FU. Expanding on this mechanism, Capecitabine is metabolized in the liver and converted into 5-FU at the tumor site through a three-step enzymatic process. The enzyme thymidine phosphorylase facilitates the final step and is more abundant in tumor cells than in normal cells, allowing targeted drug action. The active form, 5-FU, subsequently inhibits thymidylate synthase, disrupting DNA synthesis and repair and leading to cancer cell death. Capecitabine is a targeted cancer treatment, but it can also result in several side effects. Apart from the myelosuppression above and gastrointestinal disturbances, patients might experience alopecia, dermatological reactions, and, in some cases, cardiotoxicity, which necessitates careful dose management and vigilant medical supervision. Such side effects underscore the importance of individualized treatment planning, especially for patients with compromised renal function[51].

This prodrug is processed and excreted mainly through renal pathways, with 96% of its dosage identifiable in the urine. The utilization of capecitabine in patients with advanced CKD or ESKD, particularly those undergoing HD, has been explored in limited clinical studies. One notable investigation by Jhaveri *et al*[52] included 12 participants with severe CKD or ESKD (with a CC less than 30 mL/min), among whom two received HD and were administered capecitabine. This cohort exhibited minimal toxicity, indicating the relative safety of the drug. For ESKD patients, the regimen typically involves a dosage reduction to approximately 55% of the standard amount. Despite such dose modulation, patients showed a favorable response to the treatment. The research also examined the pharmacokinetics of capecitabine, recommending a 50% reduction in dosage for similar patients[52]. Given the lack of data and the need for dosage adjustments, stringent monitoring of adverse effects such as myelosuppression, hand-foot syndrome, and diarrhea is imperative after the commencement of treatment.

Methotrexate

Methotrexate (MTX) operates by targeting and inhibiting the enzyme dihydrofolate reductase, which is crucial in the folic acid metabolic pathway. This pathway is essential for producing the building blocks of DNA and RNA, such as purines and pyrimidines. By blocking dihydrofolate reductase, MTX reduces tetrahydrofolate, disrupting DNA, RNA, and protein synthesis. This disruption mainly affects rapidly dividing cells, such as cancer cells. In addition to its use in treating cancer, MTX is also used for treating certain autoimmune conditions due to its ability to diminish inflammatory responses[53].

The broad action of MTX on cell division also accounts for its side effects. These include gastrointestinal discomfort, manifesting as nausea or vomiting, mucositis, or inflammation of the mucous lining. Its impact on the bone marrow can lead to myelosuppression, resulting in diminished blood cell production and elevated risks of infection, anemia, and bleeding complications. Prolonged usage might contribute to liver damage, as indicated by increased liver enzymes, and potentially advance to fibrosis or cirrhosis in severe instances. Although less frequent, pulmonary issues such as breathlessness or persistent cough can signify pulmonary toxicity. Renal effects are also noteworthy, particularly at higher dosages, as they can cause an accumulation of the drug, heightening its toxic effects. This necessitates vigilant monitoring and potential dose modifications, especially in individuals with renal challenges[53].

MTX, with a molecular weight of 454.4 Da, is a derivative of folic acid and is an antimetabolite. Its elimination is primarily renal-based and depends significantly on the administered dose and the method of administration. When given intravenously, approximately 90% of MTX is excreted unchanged from the body within the first day, and less than 10% is biliary excreted. With the aid of aldehyde oxidase, the liver produces the significant metabolite 7-hydroxy MTX. For patients receiving lower doses of MTX (under 30 mg/m^2), the drug's half-life in the final elimination phase ranges from 3

to 10 hours. However, this extends to 8 to 15 hours in those receiving higher doses. The interaction of MTX with other drugs that target other excretion pathways can elevate its serum concentrations. Notably, nonsteroidal anti-inflammatory drugs can affect the renal clearance of MTX, potentially leading to increased toxicity. High-dose MTX, which is used in hematology (up to 6 g/day), can cause adverse drug reactions (ADRs), such as hematuria and acute kidney injury. MTX metabolites may crystallize in the renal tubules during therapy. To counter this, strategies such as intensive hydration and urine alkalization (targeting a pH of 6.5-7.0) are employed, for instance, using sodium bicarbonate or acetazolamide, less preferably in CKD. Acute renal failure, a risk factor particularly at doses exceeding 1000 mg/m^2, can impair MTX elimination, exacerbating ADRs, the likelihood of which increases with dosage[54].

In breast cancer therapy (such as the CMF regimen), the MTX dose is generally lower. However, cases such as the one reported by Langleben *et al*[55] show severe toxicity after initial administration in breast cancer treatment. Reducing this toxicity may be achieved through high-flux dialysis conducted daily[56]. In patients with ESKD, the use of MTX is advised against if alternatives are available. In HD patients, a 75% dose reduction is recommended[37].

Anthracyclines

The guidelines from the National Comprehensive Cancer Network (NCCN), European Society for Medical Oncology, and American Society of Clinical Oncology suggest that patients who have ER+/PR+/HER2+ invasive breast cancer and positive lymph nodes should undergo an adjuvant chemotherapy regimen that includes anthracycline and CTX, followed by taxanes and trastuzumab (AC to TH)[36]. The anthracyclines commonly used in breast cancer chemotherapy include doxorubicin and epirubicin[57].

The production of hydroxyl free radicals by anthracyclines is linked to both anticancer properties and potential harm to healthy tissues. The primary adverse effects that limit the dosage of anthracyclines include acute myelosuppression and cumulative dose-related cardiotoxicity. Cardiomyopathy induced by anthracyclines is often irreversible, potentially leading to clinical congestive heart failure[58]. Doxorubicin and epirubicin are removed mainly by the liver and, to a lesser degree, are excreted by the kidneys (15% and 10%, respectively)[59]. Data on the pharmacokinetics of doxorubicin in patients with renal insufficiency are currently limited[41]. Since doxorubicin and its primary active metabolite, doxorubicin, are not predominantly excreted, the dose of doxorubicin should not be modified in renal insufficiency patients[60].

Although the AUCs of doxorubicin and doxorubicin are greater in renal insufficiency patients than in patients with normal renal function, the half-lives of these two compounds are the same in both patient groups[61]. Therefore, dose reduction of doxorubicin in dialysis patients is not recommended[37]. There are currently limited data on epirubicin pharmacokinetics in ESRD patients on HD. Although dose reduction should be considered in patients with a CC < 30 mL/min, studies on the effectiveness of a reduced dose are limited[59]. A case report presented by Gori *et al*[62] described a patient with early breast cancer on HD who tolerated epirubicin without any adverse effects, including leukopenia, thrombocytopenia, or cardiotoxicity.

Cisplatin

Cisplatin belongs to platinum drugs that alkylate DNA by forming platinum-DNA adducts, leading to DNA damage, G1/S arrest, and apoptosis[63]. Cisplatin is not routinely used for breast cancer treatment, and the feasibility of cisplatin-based regimens has been confirmed in non-breast cancer patients. There is currently no data concerning the safety and efficacy of cisplatin in dialyzed breast cancer patients[59]. However, cisplatin can be an effective therapy for hereditary BRCA-1-mutated breast cancer and sporadic TBNC because they share features suggesting common pathogenesis[64]. Despite not being a standard therapeutic option for TBNC at present, there is growing interest in the potential of cisplatin, with 22 active clinical trials investigating its use, either as a standalone therapy or in combination with other treatments[65]. Although cisplatin has been available for more than 40 years, we are still struggling with severe dose-limiting side effects, particularly nephrotoxicity, which can affect dosing in approximately 30%-40% of patients[66]. The nephrotoxicity caused by cisplatin is dose-dependent, and the renal failure it induces, typically manifesting as acute tubular necrosis, is often reversible[13]. However, there are case reports in which patients developed permanent renal failure after the use of neoadjuvant cisplatin[67]. Cisplatin is predominantly eliminated through the kidney (approximately 90%)[37]. Although the use of cisplatin in patients with CKD should be avoided, it may still be used for patients with ESRD on dialysis[59]. Dose adjustments must be made in patients with ESRD on dialysis due to Cisplatin's ability to form solid and irreversible bonds with plasma proteins[37]. Tomita *et al*[68] recommended dose adjustment and administration immediately before dialysis sessions. In contrast, since the rapid elimination of free cisplatin during dialysis is not compensated by the portion of the drug complexed with protein, Janus *et al*[41] recommend administering a reduced dose of 25%-50% after dialysis.

Vinorelbine

Vinorelbine is an antimitotic anticancer agent, and its primary mechanism of action is related to the inhibition of microtubule dynamics, leading to mitotic arrest and cell death[69]. Combination chemotherapy comprising vinorelbine and doxorubicin has demonstrated effectiveness in treating advanced breast cancer, yielding response rates between 57% and 74% when used as first-line therapy[70]. The drug is eliminated mainly through the liver; only 8% of the administered dose is recovered unchanged from the urine. Vinorelbine is mainly eliminated through the liver, with only 8% of the administered dose recovered unchanged from the urine[71].

However, the superior efficacy of paclitaxel and docetaxel has led to taxane and anthracycline-based chemotherapies becoming the standard first-line treatment for metastatic breast cancer[70]. Janus *et al*[41] recommended reducing the initial dose of vinorelbine to 20 mg/m^2/week. The pharmacokinetic data associated with vinorelbine in HD patients have

not been studied; therefore, administering vinorelbine after HD sessions or on non-dialysis days is recommended.

HER-2 BASED THERAPIES

Approximately 20% of early breast cancers express HER2, and more than half of these patients are expected to progress without HER2-targeted therapy[72]. HER2-directed therapies have improved survival.

Anti-Her2 monoclonal antibodies and conjugates

Trastuzumab: Trastuzumab is a recombinant monoclonal antibody that binds the extracellular domain of HER2. Trastuzumab binds to HER2 receptors on breast cancer cells, leading to downstream heterodimerization, phosphorylation pathways, and ultimately, cell cycle arrest through AKT inhibition and antibody-dependent cell cytotoxicity in HER2-overexpressing breast cancer cells[73,74]. The efficacy of trastuzumab is comparable to that of endogenous immunoglobulins (Igs). It has low systemic clearance, a low volume of distribution, a long half-life (about 28 days), and little to no known drug-drug interactions. It is cleared by the Fc receptor-mediated IgG clearance mechanism[75,76].

Cardiotoxicity is a known concern associated with trastuzumab use and remains the primary reason for trastuzumab discontinuation in patients[77]. To our knowledge, there are no reports of trastuzumab-induced nephrotoxicity, although cases have been reported when trastuzumab was combined with other chemotherapeutic agents[78]. The product label suggests no dosage adjustment for mild to moderate renal dysfunction. Although no information exists regarding dosage adjustment in HD patients, this treatment is well tolerated in chronic renal failure and ESRD patients on HD[76,79,80] After analysis of the Food and Drug Administration adverse event reporting system, renal events (10%) included proteinuria, acute kidney injury, elevated serum creatinine, and electrolyte imbalances. However, whether such events were from concurrent or prior chemotherapy was unclear. Russo *et al*[81], in a study including 499 patients with ERB2+ early breast cancer, reported increased cardiotoxicity from trastuzumab in patients with renal dysfunction. Similar results were found in another study[82]. Notably, all the patients in this study by Russo *et al*[81] were exposed to prior chemotherapy.

Ado-trastuzumab-emtansine: It is an antibody-drug conjugate of trastuzumab and the cytotoxic agent emtansine (DM1), a microtubule inhibitor[83]. It is used in HER2+ve metastatic breast cancer patients who progress after therapy with trastuzumab and taxanes. It has a similar distribution volume to trastuzumab but a shorter half-life (about 4 days) and is mainly cleared by the liver with minimal renal elimination[84,85]. Although there is minimal data regarding its use in chronic renal failure and HD patients, individual case reports on its safe use and lack of dosage adjustment[80,86].

The package insert recommends no dosage adjustments for CrCl ≥ 30 mL/minute. Hakroush *et al*[87] reported a case of focal segmental glomerulosclerosis after the patient started trastuzumab-emtansine (T-DM1). That improved after drug discontinuation. However, further large-scale clinical studies and post-marking analysis are needed to determine its safety in treating renal impairment. Pertuzumab is a recombinant human monoclonal antibody that targets the extracellular domain of HER2 but has a different effect than trastuzumab. It blocks the dimerization of HER2 and is known to work synergistically with trastuzumab[88].

Pertuzumab: It is used with trastuzumab in patients with locally advanced, inflammatory, early-stage, or metastatic HER2+ breast cancer. Like other monoclonal antibodies, its mechanism of elimination is minimally dependent on kidney function[89]. The NeoSphere, TRYPHAENA, and CLEOPATRA trials, which included pertuzumab use, did not demonstrate renal toxicity[90-92]. It was safely tolerated in individual case reports on patients with chronic renal failure and HD[76,93].

Margetuximab: It is a chimeric Fc-engineered monoclonal antibody that binds to HER2 with higher affinity than trastuzumab[94]. It is approved for the treatment of metastatic HER2+ breast cancer patients who have failed prior HER2-based therapies[95]. It is metabolized to smaller peptides by proteases, and no dosage adjustment is recommended for patients with mild to moderate renal impairment[94]. To our knowledge, no studies report its use in renal failure and dialysis patients.

Anti-HER2 tyrosine kinase inhibitors

Lapatinib: It is a reversible dual tyrosine kinase inhibitor that inhibits HER2 and EGFR by binding to the intracellular domain of the receptor and inhibiting cell growth[96,97]. It is approved for use in treating metastatic HER2+ breast cancer with trastuzumab or capecitabine[98]. The liver clears it with < 2% renal elimination. In a study of 11 ESRD patients with breast cancer by Pai *et al*[99], lapatinib was determined to be safe. Another case report determined its safety when combined with letrozole[26]. However, large-scale clinical trials investigating the use of lapatinib in chronic renal failure and HD patients still need to be completed.

Neratinib: It is an irreversible tyrosine kinase inhibitor of the HER1, HER2, and HER4 receptors and is approved for use in advanced HER2+ breast cancer patients[100]. Studies have also suggested its effectiveness in controlling and preventing brain metastasis in this population. Cases of acute kidney injury are likely secondary to diarrhea, which is the most common treatment-related adverse effect[101]. The package insert does not provide dose adjustment information for patients with renal function impairment, but renal function does not significantly impact neratinib pharmacokinetics. Data regarding its use in renal failure and HD patients must be included. The summary of key considerations for administering systemic therapies in breast cancer patients on hemodialysis is given in Table 1.

Table 1 Summary of key considerations for administering systemic therapies in breast cancer patients on hemodialysis

Drug	Class	Use in breast cancer	Dose adjustment in HD	Key considerations for ESRD on HD
Tamoxifen	Hormone therapy	ER-positive cancers	Yes	Monitor efficacy due to altered metabolism in HD. Reduced dose may be required
Anastrozole	Aromatase inhibitor	ER-positive cancers	Yes	Reduced clearance in HD; dose modification necessary. Monitor for reduced efficacy or increased toxicity
Letrozole	Aromatase inhibitor	ER-positive cancers	Yes	Adjust dosage for renal impairment. Monitor for adverse effects
Exemestane	Aromatase inhibitor	ER-positive cancers	Yes	Use with caution in HD. Limited data; consider alternative therapies
Cyclophosphamide	Alkylating agent	Various	Yes	Requires dose reduction. Administer post-HD due to renal excretion
Doxorubicin	Anthracycline	Various	Yes	Moderate dose reduction advised. Cardiotoxicity and clearance considerations. Administer on non-dialysis days
Paclitaxel	Taxane	Various	No	Generally safe without dose adjustment. Monitor for neuropathy and hypersensitivity reactions
Docetaxel	Taxane	Various	Yes (limited data)	Data on dialysis patients limited; likely requires dose adjustment. Monitor for neutropenia and fluid retention
Gemcitabine	Nucleoside analog	Various	No	Standard doses can be used; monitor for myelosuppression and pulmonary toxicity
Carboplatin	Platinum compound	Various	Yes	Dose adjustment based on renal function using the Calvert formula. Administer post-HD for optimal clearance
Methotrexate	Antimetabolite	Various	Yes	Contraindicated in high doses; significant dose reduction required. Avoid if possible
Trastuzumab	HER2-targeted therapy	HER2-positive cancers	No	Monitor for cardiotoxicity; minimal renal impact. Safe in ESRD on HD
Lapatinib	Tyrosine kinase inhibitor	HER2-positive cancers	Yes (limited data)	Safe in ESRD; dosage adjustments may be needed. Limited data available
Atezolizumab	Immunotherapy	Triple-negative breast cancer	Yes (limited data)	Limited data on ESRD patients. Monitor closely for immune-related adverse events
Vinorelbine	Antimitotic agent	Advanced breast cancer	Yes	Reduced initial dose recommended. Eliminated mainly through the liver, but renal adjustment necessary
Capecitabine	Prodrug to 5-FU	Various	Yes	Significant reduction in dosage needed. Monitor closely for toxicity, especially hand-foot syndrome and diarrhea
Fulvestrant	Hormone therapy	ER-positive cancers	No	No dose adjustment needed. Safe to use in ESRD patients on HD
Megestrol acetate	Progestin, antineoplastic	Cancer cachexia, appetite stimulant	No	Monitor for thrombosis risk, especially in ESRD patients
CDK 4/6 inhibitors (palbociclib, ribociclib, abemaciclib)	CDK 4/6 inhibitors	HR-positive metastatic breast cancers	Limited data	No clear dose adjustments; monitor for increased serum creatinine and potential nephroprotective effects
Cisplatin	Platinum-based chemotherapy	BRCA-1-mutated and TNBC	Yes	High risk of nephrotoxicity; use cautiously and with dose adjustments. Preferably administered immediately before HD sessions
5-FU	Antimetabolite	Various	Yes	Administer post-HD

5-FU: 5-fluorouracil; HD: Hemodialysis; ESRD: End-stage renal disease; ER: Estrogen receptor; HR: Hazard ratio; HER2: Human epidermal growth factor receptor 2; CDK: Cyclin-dependent kinase; TNBC: Triple-negative breast cancer.

IMMUNE CHECKPOINT INHIBITORS

ESRD poses significant challenges for cancer treatment due to altered drug pharmacokinetics and a heightened risk of toxicity. Immunotherapy has radically improved outcomes in patients with various malignancies, including breast cancer, but evidence in patients with ESRD is lacking[102]. There are critical knowledge gaps regarding the safety,

efficacy, and pharmacokinetics of novel immunotherapies in this population. Immunotherapy aims to stimulate the body's own immune system to identify and destroy cancer cells[55]. The major classes of immune checkpoint inhibitors include cancer vaccines and adoptive cell transfer.

In breast cancer, checkpoint inhibitors target regulatory molecules on T cells or cancer cells to enhance antitumor immunity. Commonly used checkpoint agents include cytotoxic T-lymphocyte-associated antigen 4, programmed cell death protein 1 (PD-1), and its ligand PD-L1[103]. Vaccines boost immune memory against tumor antigens, while adoptive cell transfer involves engineering and growing large numbers of antitumor lymphocytes *ex vivo* before re-infusing them[104]. However, since ESRD leads to the accumulation of immunotherapies and their metabolites, which may increase toxicity, varying renal clearance levels among different agents necessitate individual dosage adjustments. However, the data are currently minimal. General principles include avoiding nephrotoxic drugs, adjusting doses based on estimated CC, and increasing toxicity monitoring.

The PD-L1 inhibitor atezolizumab was recently approved for use in treating metastatic TBNC based on clinical trials showing efficacy[103], although data specific to the ESRD population are minimal, with less than 1% representation in pivotal studies; moreover, no dedicated ESRD-focused trials have examined atezolizumab. Preliminary case reports show potential for benefit[105]; however, appropriate dosing for patients with possible uremia-induced immune dysfunction has yet to be established, and pharmacokinetic data are lacking[106]. In addition, the risk of adverse inflammatory events provoked by checkpoint inhibition may be elevated relative to that associated with normal renal function, necessitating quantification within ESRD patients to allow risk mitigation and predictive biomarker strategies; hence, further research centered on therapeutic outcomes, side effect profiles, and ideal pharmacokinetically derived regimens for atezolizumab use in ESRD patients with advanced breast cancer is critical to guide evidence-based practice for this subset of oncology patients with high unmet needs.

Similarly, other checkpoint inhibitors overall have demonstrated survival benefits in advanced breast cancer patients, especially those with triple-negative and HER2+ subtypes[107]. However, the data available to guide usage in ESRD patients is minimal. A small study of nivolumab in advanced non-small cell lung cancer dialysis patients reported comparable efficacy to non-dialysis historical controls with increased but manageable toxicity[108]. Minimal breast cancer data exist. Overall, checkpoint inhibitors appear feasible for treating ESRD, but more extensive prospective studies are desperately needed to clarify their safe dosing and efficacy, especially in breast cancer subgroups.

Cancer vaccines and adoptive cell transfer have primarily not been studied for breast cancer in the context of ESRD. Therefore, robust clinical trials are vital to clarify the expected outcomes with these approaches. Without solid evidence, clinicians are guided by dosing recommendations based primarily on pharmacokinetic data. The NCCN guidelines advise considering reduced doses for multiple immunotherapies in severe renal dysfunction patients but do not give specific quantitative advice. The Kidney Disease Improving Global Outcomes guidelines also highlight the general need for dose reductions without any definitive recommendations[102]. Additional research is vital to establish definitive dosing and safety guidelines for prescribing different immunotherapies to ESRD patients.

PARP INHIBITORS

PARP inhibitors (*e.g.*, olaparib, talazoparib) target the DNA repair enzyme PARP, which helps repair single-strand DNA breaks. By inhibiting this, they cause double-strand breaks when DNA replicates. Cancer cells with mutations in BRCA1/2 or other homologous recombination deficiency have existing defects in the ability to repair double-strand DNA breaks. Thus PARP inhibitors are especially toxic to these cells[109].

Olaparib and talazoparib are PARP inhibitor drugs that have been approved as single-agent therapies (monotherapies) for metastatic or locally advanced HER2-negative breast cancer in patients with inherited mutations in the *BRCA* genes. Specifically, approval has been granted for cases where the *BRCA* mutation is known or suspected to be deleterious[110]. Studies have shown that impaired kidney function significantly alters the pharmacokinetics of the PARP inhibitor olaparib, resulting in increased overall exposure and peak concentrations in the body[111]. While increased adverse events were not observed, the substantially higher olaparib exposure levels associated with renal impairment could potentially lead to heightened toxicity risks, especially hematologic side effects, over time[112].

Consequently, dose reductions are recommended when administering olaparib to patients with moderate kidney dysfunction. If dose adjustments are necessary during treatment, the estimated glomerular filtration rate calculated from serum creatinine levels can sometimes overestimate the actual kidney function in these patients[113]; the aforementioned applies also to talazoparib, as significantly increased exposure combined with decreased clearance of the drug is seen in patients with impaired renal function, dose adjustments downward are recommended if treating those with moderate to severe renal impairment to mitigate likely increased toxicity[114]. Currently, there are no solid guidelines established for PARP inhibitor dosing or administration specifically adapted for ESRD patients. More research is still needed to confirm the optimal therapeutic approach to PARP inhibition in breast cancer patients with significantly reduced kidney function and ESRD patients.

CONCLUSION

The altered pharmacokinetics in these patients necessitate a tailored approach for each therapeutic agent, ensuring the best possible outcomes while minimizing adverse effects. In this literature review, we have discussed most of the drugs used in the treatment of breast cancer and whether dose adjustment needs to be made in ESRD patients on HD. However,

it is crucial to acknowledge certain limitations in our study.

In summary, the approach to breast cancer treatment in individuals with advanced renal failure undergoing HD demands a sophisticated comprehension of the pharmacokinetic changes due to renal dysfunction. Hormonal treatments such as tamoxifen and inhibitors of aromatase (anastrozole, letrozole, exemestane) require prudent management given their liver metabolism and renal excretion, with inhibitors of aromatase needing adjustments to avert toxicity. Metabolized *via* CYP3A4, fulvestrant typically does not necessitate alterations, underscoring the diversity in managing different therapies. Megestrol acetate, employed for its anticancer effects and to address cachexia in cancer, necessitates careful prescribing due to an increased risk of clotting in this demographic.

Regarding chemotherapeutic agents and therapies targeting HER2, they further exemplify the intricacies of administering breast cancer care to patients with ESRD. CTX, doxorubicin, gemcitabine, and carboplatin each require specific considerations for dosage adjustments or scheduling of dialysis procedures to maximize treatment benefits while reducing unwanted effects. On the other hand, therapies targeting HER2, such as trastuzumab, lapatinib, and pertuzumab, seem comparatively secure without significant dosage modification, although more investigation is advised to confirm these guidelines. As an emerging avenue in cancer therapy, immunotherapy demands more research to ascertain its efficacy and safety in ESRD patients. Hence, a customized strategy for each medication, informed by their pharmacokinetic profiles in advanced renal failure, is crucial for optimizing patient outcomes while minimizing potential risks in this susceptible population.

The review did not provide information about the role of radiation and surgery in breast cancer patients with HD. This omission limits the holistic understanding of treatment modalities for this patient population. A notable limitation is the scarcity of data on the role of certain drugs in breast cancer patients with HD. While we discussed most drugs, some medications lack sufficient research in this patient group, highlighting an area for future investigation. Generalizability, publication bias, methodological quality of included studies, and inclusion/exclusion criteria should be acknowledged for a more comprehensive interpretation of the review's findings.

FOOTNOTES

Author contributions: Khan S, Araji G, Yetiskul E, Keesari PR, Haddadin F, Khamis Z, Chowdhry V, Afif S, Dhar M, and El-Sayegh S designed the research study and performed the research, and contributed new reagents and analytic tools; Khan S, Araji G, Yetiskul E, Keesari PR, Haddadin F, Khamis Z, Chowdhry V, Niazi M, Afif S, Dhar M, and El-Sayegh S analyzed the data and wrote the manuscript; and all authors have read and approved the final manuscript.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

Country of origin: United States

ORCID number: Salman Khan 0000-0002-4828-2794; Ekrem Yetiskul 0009-0003-9185-6356.

S-Editor: Wang JJ
L-Editor: A
P-Editor: Zhao YQ

REFERENCES

1 **Ryu JH**, Kim H, Kim KH, Hann HJ, Ahn HS, Lee S, Kim SJ, Kang DH, Choi KB, Ryu DR. Improving survival rate of Korean patients initiating dialysis. *Yonsei Med J* 2015; **56**: 666-675 [PMID: 25837171 DOI: 10.3349/ymj.2015.56.3.666]

2 **Maisonneuve P**, Agodoa L, Gellert R, Stewart JH, Buccianti G, Lowenfels AB, Wolfe RA, Jones E, Disney AP, Briggs D, McCredie M, Boyle P. Cancer in patients on dialysis for end-stage renal disease: an international collaborative study. *Lancet* 1999; **354**: 93-99 [PMID: 10408483 DOI: 10.1016/S0140-6736(99)06154-1]

3 **Stewart JH**, Vajdic CM, van Leeuwen MT, Amin J, Webster AC, Chapman JR, McDonald SP, Grulich AE, McCredie MR. The pattern of excess cancer in dialysis and transplantation. *Nephrol Dial Transplant* 2009; **24**: 3225-3231 [PMID: 19589786 DOI: 10.1093/ndt/gfp331]

4 **Lin HF**, Li YH, Wang CH, Chou CL, Kuo DJ, Fang TC. Increased risk of cancer in chronic dialysis patients: a population-based cohort study in Taiwan. *Nephrol Dial Transplant* 2012; **27**: 1585-1590 [PMID: 21862456 DOI: 10.1093/ndt/gfr464]

5 **Butler AM**, Olshan AF, Kshirsagar AV, Edwards JK, Nielsen ME, Wheeler SB, Brookhart MA. Cancer incidence among US Medicare ESRD patients receiving hemodialysis, 1996-2009. *Am J Kidney Dis* 2015; **65**: 763-772 [PMID: 25662835 DOI: 10.1053/j.ajkd.2014.12.013]

6 **Taborelli M**, Toffolutti F, Del Zotto S, Clagnan E, Furian L, Piselli P, Citterio F, Zanier L, Boscutti G, Serraino D; Italian Transplant & Cancer Cohort Study. Increased cancer risk in patients undergoing dialysis: a population-based cohort study in North-Eastern Italy. *BMC Nephrol* 2019; **20**: 107 [PMID: 30922296 DOI: 10.1186/s12882-019-1283-4]

7 **Zannetti A**. Breast Cancer: From Pathophysiology to Novel Therapeutic Approaches 2.0. *Int J Mol Sci* 2023; **24** [PMID: 36768866 DOI: 10.3390/ijms24032542]

8 **Lin MY**, Kuo MC, Hung CC, Wu WJ, Chen LT, Yu ML, Hsu CC, Lee CH, Chen HC, Hwang SJ. Association of dialysis with the risks of cancers. *PLoS One* 2015; **10**: e0122856 [PMID: 25874862 DOI: 10.1371/journal.pone.0122856]

9 **Iff S**, Craig JC, Turner R, Chapman JR, Wang JJ, Mitchell P, Wong G. Reduced estimated GFR and cancer mortality. *Am J Kidney Dis* 2014; **63**: 23-30 [PMID: 23993153 DOI: 10.1053/j.ajkd.2013.07.008]

10 Breast Cancer Treatment (PDQ®): Patient Version. 2024 Feb 26. In: PDQ Cancer Information Summaries [Internet]. Bethesda (MD): National Cancer Institute (US); 2002– [PMID: 26389406]

11 **Korde LA**, Somerfield MR, Carey LA, Crews JR, Denduluri N, Hwang ES, Khan SA, Loibl S, Morris EA, Perez A, Regan MM, Spears PA, Sudheendra PK, Symmans WF, Yung RL, Harvey BE, Hershman DL. Neoadjuvant Chemotherapy, Endocrine Therapy, and Targeted Therapy for Breast Cancer: ASCO Guideline. *J Clin Oncol* 2021; **39**: 1485-1505 [PMID: 33507815 DOI: 10.1200/JCO.20.03399]

12 **Allison KH**, Hammond MEH, Dowsett M, McKernin SE, Carey LA, Fitzgibbons PL, Hayes DF, Lakhani SR, Chavez-MacGregor M, Perlmutter J, Perou CM, Regan MM, Rimm DL, Symmans WF, Torlakovic EE, Varella L, Viale G, Weisberg TF, McShane LM, Wolff AC. Estrogen and Progesterone Receptor Testing in Breast Cancer: ASCO/CAP Guideline Update. *J Clin Oncol* 2020; **38**: 1346-1366 [PMID: 31928404 DOI: 10.1200/JCO.19.02309]

13 **Sommer G**, Kopsa H, Zazgornik J, Salomonowitz E. Breast calcifications in renal hyperparathyroidism. *AJR Am J Roentgenol* 1987; **148**: 855-857 [PMID: 3554917 DOI: 10.2214/ajr.148.5.855]

14 **Cooper RA**, Berman S. Extensive breast calcification in renal failure. *J Thorac Imaging* 1988; **3**: 81-82 [PMID: 3361629 DOI: 10.1097/00005382-198804000-00010]

15 **Parfitt AM**. Soft-tissue calcification in uremia. *Arch Intern Med* 1969; **124**: 544-556 [PMID: 4899444 DOI: 10.1001/archinte.124.5.544]

16 **Castellanos MR**, Paramanathan K, El-Sayegh S, Forte F, Buchbinder S, Kleiner M. Breast cancer screening in women with chronic kidney disease: the unrecognized effects of metastatic soft-tissue calcification. *Nat Clin Pract Nephrol* 2008; **4**: 337-341 [PMID: 18414461 DOI: 10.1038/ncpneph0804]

17 **Hall DJ**, Gentile LF, Duckworth LV, Shaw CM, Singhal D, Spiguel LR. Calciphylaxis of the Breast: A Case Report and Literature Review. *Breast J* 2016; **22**: 568-572 [PMID: 27332900 DOI: 10.1111/tbj.12632]

18 **Basu P**, Leong LCH, Tan BY, Tan BKT. Breast calcifications in patients with end-stage renal disease. *Breast J* 2019; **25**: 515-516 [PMID: 30973661 DOI: 10.1111/tbj.13272]

19 **Van Berkel B**, Van Ongeval C, Van Craenenbroeck AH, Pottel H, De Vusser K, Evenepoel P. Prevalence, progression and implications of breast artery calcification in patients with chronic kidney disease. *Clin Kidney J* 2022; **15**: 295-302 [PMID: 35145644 DOI: 10.1093/ckj/sfab178]

20 **Castellanos M**, Varma S, Ahern K, Grosso SJ, Buchbinder S, D'Angelo D, Raia C, Kleiner M, Elsayegh S. Increased breast calcifications in women with ESRD on dialysis: implications for breast cancer screening. *Am J Kidney Dis* 2006; **48**: 301-306 [PMID: 16860197 DOI: 10.1053/j.ajkd.2006.05.001]

21 **Desta Z**, Ward BA, Soukhova NV, Flockhart DA. Comprehensive evaluation of tamoxifen sequential biotransformation by the human cytochrome P450 system in vitro: prominent roles for CYP3A and CYP2D6. *J Pharmacol Exp Ther* 2004; **310**: 1062-1075 [PMID: 15159443 DOI: 10.1124/jpet.104.065607]

22 **Crewe HK**, Notley LM, Wunsch RM, Lennard MS, Gillam EM. Metabolism of tamoxifen by recombinant human cytochrome P450 enzymes: formation of the 4-hydroxy, 4'-hydroxy and N-desmethyl metabolites and isomerization of trans-4-hydroxytamoxifen. *Drug Metab Dispos* 2002; **30**: 869-874 [PMID: 12124303 DOI: 10.1124/dmd.30.8.869]

23 **Langenegger T**, Wahl P, Schiesser D, Thürlimann B. Plasma levels of tamoxifen, N-desmethyl tamoxifen and anastrozole in a patient with metastatic breast cancer and chronic hemodialysis. *Breast Cancer Res Treat* 2006; **100**: 177-181 [PMID: 16688477 DOI: 10.1007/s10549-006-9243-7]

24 **Kharb R**, Haider K, Neha K, Yar MS. Aromatase inhibitors: Role in postmenopausal breast cancer. *Arch Pharm (Weinheim)* 2020; **353**: e2000081 [PMID: 32449548 DOI: 10.1002/ardp.202000081]

25 **National Library of Medicine**. Letrozole. [cited 15 January 2024]. Available from: https://pubchem.ncbi.nlm.nih.gov/compound/Letrozole

26 **Piacentini F**, Omarini C, Barbieri E. Lapatinib and renal impairment: a case report. *Tumori* 2013; **99**: e134-e135 [PMID: 24158084 DOI: 10.1177/030089161309900334]

27 **Robertson JF**, Harrison M. Fulvestrant: pharmacokinetics and pharmacology. *Br J Cancer* 2004; **90** Suppl 1: S7-10 [PMID: 15094758 DOI: 10.1038/sj.bjc.6601630]

28 **Peng J**, Sengupta S, Jordan VC. Potential of selective estrogen receptor modulators as treatments and preventives of breast cancer. *Anticancer Agents Med Chem* 2009; **9**: 481-499 [PMID: 19519291 DOI: 10.2174/187152009788451833]

29 **Bines J**, Dienstmann R, Obadia RM, Branco LGP, Quintella DC, Castro TM, Camacho PG, Soares FA, Costa MEF. Activity of megestrol acetate in postmenopausal women with advanced breast cancer after nonsteroidal aromatase inhibitor failure: a phase II trial. *Ann Oncol* 2014; **25**: 831-836 [PMID: 24615412 DOI: 10.1093/annonc/mdu015]

30 **Wazny LD**, Nadurak S, Orsulak C, Giles-Smith L, Tangri N. The Efficacy and Safety of Megestrol Acetate in Protein-Energy Wasting due to Chronic Kidney Disease: A Systematic Review. *J Ren Nutr* 2016; **26**: 168-176 [PMID: 26776251 DOI: 10.1053/j.jrn.2015.11.002]

31 **DiRocco DP**, Bisi J, Roberts P, Strum J, Wong KK, Sharpless N, Humphreys BD. CDK4/6 inhibition induces epithelial cell cycle arrest and ameliorates acute kidney injury. *Am J Physiol Renal Physiol* 2014; **306**: F379-F388 [PMID: 24338822 DOI: 10.1152/ajprenal.00475.2013]

32 **Sledge GW Jr**, Toi M, Neven P, Sohn J, Inoue K, Pivot X, Burdaeva O, Okera M, Masuda N, Kaufman PA, Koh H, Grischke EM, Frenzel M, Lin Y, Barriga S, Smith IC, Bourayou N, Llombart-Cussac A. MONARCH 2: Abemaciclib in Combination With Fulvestrant in Women With HR+/HER2- Advanced Breast Cancer Who Had Progressed While Receiving Endocrine Therapy. *J Clin Oncol* 2017; **35**: 2875-2884 [PMID: 28580882 DOI: 10.1200/JCO.2017.73.7585]

33 **Chappell JC**, Turner PK, Pak YA, Bacon J, Chiang AY, Royalty J, Hall SD, Kulanthaivel P, Bonventre JV. Abemaciclib Inhibits Renal Tubular Secretion Without Changing Glomerular Filtration Rate. *Clin Pharmacol Ther* 2019; **105**: 1187-1195 [PMID: 30449032 DOI: 10.1002/cpt.1296]

34 **National Library of Medicine**. Cyclophosphamide. [cited 15 January 2024]. Available from: https://pubchem.ncbi.nlm.nih.gov/compound/Cyclophosphamide

35 **Yang L**, Zhang XC, Yu SF, Zhu HQ, Hu AP, Chen J, Shen P. Pharmacokinetics and safety of cyclophosphamide and docetaxel in a hemodialysis patient with early stage breast cancer: a case report. *BMC Cancer* 2015; **15**: 917 [PMID: 26582454 DOI: 10.1186/s12885-015-1932-3]

36 **Haubitz M**, Bohnenstengel F, Brunkhorst R, Schwab M, Hofmann U, Busse D. Cyclophosphamide pharmacokinetics and dose requirements in

patients with renal insufficiency. *Kidney Int* 2002; **61**: 1495-1501 [PMID: 11918757 DOI: 10.1046/j.1523-1755.2002.00279.x]
37 **Pedrazzoli P**, Silvestris N, Santoro A, Secondino S, Brunetti O, Longo V, Mancini E, Mariucci S, Rampino T, Delfanti S, Brugnatelli S, Cinieri S. Management of patients with end-stage renal disease undergoing chemotherapy: recommendations of the Associazione Italiana di Oncologia Medica (AIOM) and the Società Italiana di Nefrologia (SIN). *ESMO Open* 2017; **2**: e000167 [PMID: 29209521 DOI: 10.1136/esmoopen-2017-000167]
38 **Pienta KJ**. Preclinical mechanisms of action of docetaxel and docetaxel combinations in prostate cancer. *Semin Oncol* 2001; **28**: 3-7 [PMID: 11685722 DOI: 10.1053/sonc.2001.26892]
39 **National Library of Medicine**. Taxane. [cited 15 January 2024]. Available from: https://pubchem.ncbi.nlm.nih.gov/compound/Taxane
40 **Watanabe M**, Aoki Y, Tomita M, Sato T, Takaki Y, Kato N, Kikuchi M, Kase H, Tanaka K. Paclitaxel and carboplatin combination chemotherapy in a hemodialysis patient with advanced ovarian cancer. *Gynecol Oncol* 2002; **84**: 335-338 [PMID: 11812097 DOI: 10.1006/gyno.2001.6527]
41 **Janus N**, Thariat J, Boulanger H, Deray G, Launay-Vacher V. Proposal for dosage adjustment and timing of chemotherapy in hemodialyzed patients. *Ann Oncol* 2010; **21**: 1395-1403 [PMID: 20118214 DOI: 10.1093/annonc/mdp598]
42 **Plunkett W**, Huang P, Xu YZ, Heinemann V, Grunewald R, Gandhi V. Gemcitabine: metabolism, mechanisms of action, and self-potentiation. *Semin Oncol* 1995; **22**: 3-10 [PMID: 7481842]
43 **Li YF**, Fu S, Hu W, Liu JH, Finkel KW, Gershenson DM, Kavanagh JJ. Systemic anticancer therapy in gynecological cancer patients with renal dysfunction. *Int J Gynecol Cancer* 2007; **17**: 739-763 [PMID: 17309673 DOI: 10.1111/j.1525-1438.2007.00847.x]
44 **Egorin MJ**, Van Echo DA, Tipping SJ, Olman EA, Whitacre MY, Thompson BW, Aisner J. Pharmacokinetics and dosage reduction of cis-diammine(1,1-cyclobutanedicarboxylato)platinum in patients with impaired renal function. *Cancer Res* 1984; **44**: 5432-5438 [PMID: 6386150]
45 **Drugs**. com®. Carboplatin (Monograph). [cited 15 January 2024]. Available from: https://www.drugs.com/monograph/carboplatin.html
46 **Calvert AH**, Newell DR, Gumbrell LA, O'Reilly S, Burnell M, Boxall FE, Siddik ZH, Judson IR, Gore ME, Wiltshaw E. Carboplatin dosage: prospective evaluation of a simple formula based on renal function. *J Clin Oncol* 1989; **7**: 1748-1756 [PMID: 2681557 DOI: 10.1200/JCO.1989.7.11.1748]
47 **Hiraike M**, Hiraki Y, Misumi N, Hanada K, Tsuji Y, Kamimura H, Karube Y, Kashiwabara K. Pharmacokinetics of carboplatin in a hemodialysis patient with small-cell lung cancer. *Cancer Chemother Pharmacol* 2012; **69**: 845-848 [PMID: 22194156 DOI: 10.1007/s00280-011-1802-x]
48 **Heijns JB**, van der Burg ME, van Gelder T, Fieren MW, de Bruijn P, van der Gaast A, Loos WJ. Continuous ambulatory peritoneal dialysis: pharmacokinetics and clinical outcome of paclitaxel and carboplatin treatment. *Cancer Chemother Pharmacol* 2008; **62**: 841-847 [PMID: 18204842 DOI: 10.1007/s00280-007-0671-9]
49 **Zhang N**, Yin Y, Xu SJ, Chen WS. 5-Fluorouracil: mechanisms of resistance and reversal strategies. *Molecules* 2008; **13**: 1551-1569 [PMID: 18794772 DOI: 10.3390/molecules13081551]
50 **National Library of Medicine**. Fluorouracil. [cited 15 January 2024]. Available from: https://pubchem.ncbi.nlm.nih.gov/compound/Fluorouracil
51 **Walko CM**, Lindley C. Capecitabine: a review. *Clin Ther* 2005; **27**: 23-44 [PMID: 15763604 DOI: 10.1016/j.clinthera.2005.01.005]
52 **Jhaveri KD**, Flombaum C, Shah M, Latcha S. A retrospective observational study on the use of capecitabine in patients with severe renal impairment (GFR <30 mL/min) and end stage renal disease on hemodialysis. *J Oncol Pharm Pract* 2012; **18**: 140-147 [PMID: 22392964 DOI: 10.1177/1078155210390255]
53 **Tian H**, Cronstein BN. Understanding the mechanisms of action of methotrexate: implications for the treatment of rheumatoid arthritis. *Bull NYU Hosp Jt Dis* 2007; **65**: 168-173 [PMID: 17922664]
54 **National Library of Medicine**. Methotrexate. [cited 15 January 2024]. Available from: https://pubchem.ncbi.nlm.nih.gov/compound/Methotrexate
55 **Langleben A**, Hollomby D, Hand R. Case report: management of methotrexate toxicity in an anephric patient. *Clin Invest Med* 1982; **5**: 129-132 [PMID: 6288301]
56 **Murashima M**, Adamski J, Milone MC, Shaw L, Tsai DE, Bloom RD. Methotrexate clearance by high-flux hemodialysis and peritoneal dialysis: a case report. *Am J Kidney Dis* 2009; **53**: 871-874 [PMID: 19339090 DOI: 10.1053/j.ajkd.2009.01.016]
57 **Liu W**, Peng JF, Tang MJ. Individualized Treatment Analysis Of Breast Cancer With Chronic Renal Failure. *Onco Targets Ther* 2019; **12**: 7767-7772 [PMID: 31571926 DOI: 10.2147/OTT.S223729]
58 **Hortobágyi GN**. Anthracyclines in the treatment of cancer. An overview. *Drugs* 1997; **54** Suppl 4: 1-7 [PMID: 9361955 DOI: 10.2165/00003495-199700544-00003]
59 **Bednarek A**, Mykała-Cieśla J, Pogoda K, Jagiełło-Gruszfeld A, Kunkiel M, Winder M, Chudek J. Limitations of Systemic Oncological Therapy in Breast Cancer Patients with Chronic Kidney Disease. *J Oncol* 2020; **2020**: 7267083 [PMID: 32508921 DOI: 10.1155/2020/7267083]
60 **Gabizon A**, Catane R, Uziely B, Kaufman B, Safra T, Cohen R, Martin F, Huang A, Barenholz Y. Prolonged circulation time and enhanced accumulation in malignant exudates of doxorubicin encapsulated in polyethylene-glycol coated liposomes. *Cancer Res* 1994; **54**: 987-992 [PMID: 8313389]
61 **Yoshida H**, Goto M, Honda A, Nabeshima T, Kumazawa T, Inagaki J, Yamanaka N, Ota K. Pharmacokinetics of doxorubicin and its active metabolite in patients with normal renal function and in patients on hemodialysis. *Cancer Chemother Pharmacol* 1994; **33**: 450-454 [PMID: 8137454 DOI: 10.1007/BF00686499]
62 **Gori S**, Rulli A, Mosconi AM, Sidoni A, Colozza M, Crinò L. Safety of epirubicin adjuvant chemotherapy in a breast cancer patient with chronic renal failure undergoing hemodialytic treatment. *Tumori* 2006; **92**: 364-365 [PMID: 17036534 DOI: 10.1177/030089160609200421]
63 **Wang H**, Guo S, Kim SJ, Shao F, Ho JWK, Wong KU, Miao Z, Hao D, Zhao M, Xu J, Zeng J, Wong KH, Di L, Wong AH, Xu X, Deng CX. Cisplatin prevents breast cancer metastasis through blocking early EMT and retards cancer growth together with paclitaxel. *Theranostics* 2021; **11**: 2442-2459 [PMID: 33500735 DOI: 10.7150/thno.46460]
64 **Silver DP**, Richardson AL, Eklund AC, Wang ZC, Szallasi Z, Li Q, Juul N, Leong CO, Calogrias D, Buraimoh A, Fatima A, Gelman RS, Ryan PD, Tung NM, De Nicolo A, Ganesan S, Miron A, Colin C, Sgroi DC, Ellisen LW, Winer EP, Garber JE. Efficacy of neoadjuvant Cisplatin in triple-negative breast cancer. *J Clin Oncol* 2010; **28**: 1145-1153 [PMID: 20100965 DOI: 10.1200/JCO.2009.22.4725]
65 **Hill DP**, Harper A, Malcolm J, McAndrews MS, Mockus SM, Patterson SE, Reynolds T, Baker EJ, Bult CJ, Chesler EJ, Blake JA. Cisplatin-resistant triple-negative breast cancer subtypes: multiple mechanisms of resistance. *BMC Cancer* 2019; **19**: 1039 [PMID: 31684899 DOI: 10.1186/s12885-019-6278-9]

66 **Zhang J**, Ye ZW, Tew KD, Townsend DM. Cisplatin chemotherapy and renal function. *Adv Cancer Res* 2021; **152**: 305-327 [PMID: 34353441 DOI: 10.1016/bs.acr.2021.03.008]

67 **Sasaki T**, Motoyama S, Komatsuda A, Shibata H, Sato Y, Yoshino K, Wakita A, Saito H, Anbai A, Jin M, Minamiya Y. Two cases of cisplatin-induced permanent renal failure following neoadjuvant chemotherapy for esophageal cancer. *Int J Surg Case Rep* 2016; **20**: 63-67 [PMID: 26851395 DOI: 10.1016/j.ijscr.2016.01.009]

68 **Tomita M**, Aoki Y, Tanaka K. Effect of haemodialysis on the pharmacokinetics of antineoplastic drugs. *Clin Pharmacokinet* 2004; **43**: 515-527 [PMID: 15170366 DOI: 10.2165/00003088-200443080-00002]

69 **Capasso A**. Vinorelbine in cancer therapy. *Curr Drug Targets* 2012; **13**: 1065-1071 [PMID: 22594474 DOI: 10.2174/138945012802009017]

70 **Cybulska-Stopa B**, Ziobro M, Skoczek M, Kojs-Pasińska E, Cedrych I, Brandys A. Evaluation of vinorelbine-based chemotherapy as the second or further-line treatment in patients with metastatic breast cancer. *Contemp Oncol (Pozn)* 2013; **17**: 78-82 [PMID: 23788967 DOI: 10.5114/wo.2013.33779]

71 **Krikorian A**, Rahmani R, Bromet M, Bore P, Cano JP. Pharmacokinetics and metabolism of Navelbine. *Semin Oncol* 1989; **16**: 21-25

72 **O'Shaughnessy J**, Gradishar W, O'Regan R, Gadi V. Risk of Recurrence in Patients With HER2+ Early-Stage Breast Cancer: Literature Analysis of Patient and Disease Characteristics. *Clin Breast Cancer* 2023; **23**: 350-362 [PMID: 37149421 DOI: 10.1016/j.clbc.2023.03.007]

73 **Maadi H**, Wang Z. A Novel Mechanism Underlying the Inhibitory Effects of Trastuzumab on the Growth of HER2-Positive Breast Cancer Cells. *Cells* 2022; **11** [PMID: 36552857 DOI: 10.3390/cells11244093]

74 **Maadi H**, Soheilifar MH, Choi WS, Moshtaghian A, Wang Z. Trastuzumab Mechanism of Action; 20 Years of Research to Unravel a Dilemma. *Cancers (Basel)* 2021; **13** [PMID: 34298754 DOI: 10.3390/cancers13143540]

75 **Levêque D**, Gigou L, Bergerat JP. Clinical pharmacology of trastuzumab. *Curr Clin Pharmacol* 2008; **3**: 51-55 [PMID: 18690878 DOI: 10.2174/157488408783329931]

76 **Cai JH**, Zheng JH, Lin XQ, Lin WX, Zou J, Chen YK, Li ZY, Chen YX. Individualized treatment of breast cancer with chronic renal failure: A case report and review of literature. *World J Clin Cases* 2021; **9**: 10345-10354 [PMID: 34904109 DOI: 10.12998/wjcc.v9.i33.10345]

77 **Onitilo AA**, Engel JM, Stankowski RV. Cardiovascular toxicity associated with adjuvant trastuzumab therapy: prevalence, patient characteristics, and risk factors. *Ther Adv Drug Saf* 2014; **5**: 154-166 [PMID: 25083270 DOI: 10.1177/2042098614529603]

78 **Slamon D**, Eiermann W, Robert N, Pienkowski T, Martin M, Press M, Mackey J, Glaspy J, Chan A, Pawlicki M, Pinter T, Valero V, Liu MC, Sauter G, von Minckwitz G, Visco F, Bee V, Buyse M, Bendahmane B, Tabah-Fisch I, Lindsay MA, Riva A, Crown J; Breast Cancer International Research Group. Adjuvant trastuzumab in HER2-positive breast cancer. *N Engl J Med* 2011; **365**: 1273-1283 [PMID: 21991949 DOI: 10.1056/NEJMoa0910383]

79 **Micallef RA**, Barrett-Lee PJ, Donovan K, Ashraf M, Williams L. Trastuzumab in patients on haemodialysis for renal failure. *Clin Oncol (R Coll Radiol)* 2007; **19**: 559 [PMID: 17566724 DOI: 10.1016/j.clon.2007.04.008]

80 **González AF**, Garcia PE, Gastaldo AS, Simón IS, Boffil JS, Borrego MR. Safety and efficacy of trastuzumab emtansine (TDM-1) in a patient on hemodialysis for renal failure. *Cancer Treat Res Commun* 2021; **27**: 100314 [PMID: 33545569 DOI: 10.1016/j.ctarc.2021.100314]

81 **Russo G**, Cioffi G, Di Lenarda A, Tuccia F, Bovelli D, Di Tano G, Alunni G, Gori S, Faggiano P, Tarantini L. Role of renal function on the development of cardiotoxicity associated with trastuzumab-based adjuvant chemotherapy for early breast cancer. *Intern Emerg Med* 2012; **7**: 439-446 [PMID: 22714882 DOI: 10.1007/s11739-012-0794-9]

82 **Albini A**, Donatelli F, Focaccetti C, D'Elios MM, Noonan DM. Renal dysfunction and increased risk of cardiotoxicity with trastuzumab therapy: a new challenge in cardio-oncology. *Intern Emerg Med* 2012; **7**: 399-401 [PMID: 22941411 DOI: 10.1007/s11739-012-0845-2]

83 **von Minckwitz G**, Huang CS, Mano MS, Loibl S, Mamounas EP, Untch M, Wolmark N, Rastogi P, Schneeweiss A, Redondo A, Fischer HH, Jacot W, Conlin AK, Arce-Salinas C, Wapnir IL, Jackisch C, DiGiovanna MP, Fasching PA, Crown JP, Wülfing P, Shao Z, Rota Caremoli E, Wu H, Lam LH, Tesarowski D, Smitt M, Douthwaite H, Singel SM, Geyer CE Jr; KATHERINE Investigators. Trastuzumab Emtansine for Residual Invasive HER2-Positive Breast Cancer. *N Engl J Med* 2019; **380**: 617-628 [PMID: 30516102 DOI: 10.1056/NEJMoa1814017]

84 **Lu D**, Girish S, Gao Y, Wang B, Yi JH, Guardino E, Samant M, Cobleigh M, Rimawi M, Conte P, Jin JY. Population pharmacokinetics of trastuzumab emtansine (T-DM1), a HER2-targeted antibody-drug conjugate, in patients with HER2-positive metastatic breast cancer: clinical implications of the effect of covariates. *Cancer Chemother Pharmacol* 2014; **74**: 399-410 [PMID: 24939213 DOI: 10.1007/s00280-014-2500-2]

85 **Shen BQ**, Bumbaca D, Saad O, Yue Q, Pastuskovas CV, Khojasteh SC, Tibbitts J, Kaur S, Wang B, Chu YW, LoRusso PM, Girish S. Catabolic fate and pharmacokinetic characterization of trastuzumab emtansine (T-DM1): an emphasis on preclinical and clinical catabolism. *Curr Drug Metab* 2012; **13**: 901-910 [PMID: 22475269 DOI: 10.2174/138920012802138598]

86 **Natarajan SK**, Danansezhian JC, Thummar V, Mehta P. Favorable Outcome and Safety of Neoadjuvant Trastuzumab Emtansine (T-DM1) in a HER2-Positive Early Breast Cancer Patient with Severe Renal Disease on Hemodialysis Ineligible for Conventional Chemotherapy: A Case Report. *Reports* 2023; **6**: 13 [DOI: 10.3390/reports6010013]

87 **Hakroush S**, Wulf S, Gallwas J, Tampe B. Case Report: Collapsing Focal Segmental Glomerulosclerosis After Initiation of Ado-Trastuzumab Emtansine Therapy. *Front Oncol* 2021; **11**: 796223 [PMID: 34912725 DOI: 10.3389/fonc.2021.796223]

88 **Harbeck N**, Beckmann MW, Rody A, Schneeweiss A, Müller V, Fehm T, Marschner N, Gluz O, Schrader I, Heinrich G, Untch M, Jackisch C. HER2 Dimerization Inhibitor Pertuzumab - Mode of Action and Clinical Data in Breast Cancer. *Breast Care (Basel)* 2013; **8**: 49-55 [PMID: 24715843 DOI: 10.1159/000346837]

89 **Keizer RJ**, Huitema AD, Schellens JH, Beijnen JH. Clinical pharmacokinetics of therapeutic monoclonal antibodies. *Clin Pharmacokinet* 2010; **49**: 493-507 [PMID: 20608753 DOI: 10.2165/11531280-000000000-00000]

90 **Gianni L**, Pienkowski T, Im YH, Roman L, Tseng LM, Liu MC, Lluch A, Staroslawska E, de la Haba-Rodriguez J, Im SA, Pedrini JL, Poirier B, Morandi P, Semiglazov V, Srimuninnimit V, Bianchi G, Szado T, Ratnayake J, Ross G, Valagussa P. Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): a randomised multicentre, open-label, phase 2 trial. *Lancet Oncol* 2012; **13**: 25-32 [PMID: 22153890 DOI: 10.1016/S1470-2045(11)70336-9]

91 **Schneeweiss A**, Chia S, Hickish T, Harvey V, Eniu A, Hegg R, Tausch C, Seo JH, Tsai YF, Ratnayake J, McNally V, Ross G, Cortés J. Pertuzumab plus trastuzumab in combination with standard neoadjuvant anthracycline-containing and anthracycline-free chemotherapy regimens in patients with HER2-positive early breast cancer: a randomized phase II cardiac safety study (TRYPHAENA). *Ann Oncol* 2013; **24**: 2278-2284 [PMID: 23704196 DOI: 10.1093/annonc/mdt182]

92 **Swain SM**, Miles D, Kim SB, Im YH, Im SA, Semiglazov V, Ciruelos E, Schneeweiss A, Loi S, Monturus E, Clark E, Knott A, Restuccia E, Benyunes MC, Cortés J; CLEOPATRA study group. Pertuzumab, trastuzumab, and docetaxel for HER2-positive metastatic breast cancer

(CLEOPATRA): end-of-study results from a double-blind, randomised, placebo-controlled, phase 3 study. *Lancet Oncol* 2020; **21**: 519-530 [PMID: 32171426 DOI: 10.1016/S1470-2045(19)30863-0]

93 **Gaertner KM**, Poornima IG, Hilton C. Trastuzumab and pertuzumab in hemodialysis: A case report. *J Oncol Pharm Pract* 2021; **27**: 1799-1801 [PMID: 33779370 DOI: 10.1177/10781552211003641]

94 **Schlam I**, Nunes R, Lynce F. Profile of Margetuximab: Evidence to Date in the Targeted Treatment of Metastatic HER2-positive Breast Cancer. *Onco Targets Ther* 2022; **15**: 471-478 [PMID: 35509453 DOI: 10.2147/OTT.S272197]

95 **Rugo HS**, Im SA, Cardoso F, Cortes J, Curigliano G, Musolino A, Pegram MD, Bachelot T, Wright GS, Saura C, Escrivá-de-Romaní S, De Laurentiis M, Schwartz GN, Pluard TJ, Ricci F, Gwin WR 3rd, Levy C, Brown-Glaberman U, Ferrero JM, de Boer M, Kim SB, Petráková K, Yardley DA, Freedman O, Jakobsen EH, Gal-Yam EN, Yerushalmi R, Fasching PA, Kaufman PA, Ashley EJ, Perez-Olle R, Hong S, Rosales MK, Gradishar WJ; SOPHIA Study Group. Margetuximab Versus Trastuzumab in Patients With Previously Treated HER2-Positive Advanced Breast Cancer (SOPHIA): Final Overall Survival Results From a Randomized Phase 3 Trial. *J Clin Oncol* 2023; **41**: 198-205 [PMID: 36332179 DOI: 10.1200/JCO.21.02937]

96 **Nolting M**, Schneider-Merck T, Trepel M. Lapatinib. *Recent Results Cancer Res* 2014; **201**: 125-143 [PMID: 24756789 DOI: 10.1007/978-3-642-54490-3_7]

97 **Segovia-Mendoza M**, González-González ME, Barrera D, Díaz L, García-Becerra R. Efficacy and mechanism of action of the tyrosine kinase inhibitors gefitinib, lapatinib and neratinib in the treatment of HER2-positive breast cancer: preclinical and clinical evidence. *Am J Cancer Res* 2015; **5**: 2531-2561 [PMID: 26609467]

98 **Ryan Q**, Ibrahim A, Cohen MH, Johnson J, Ko CW, Sridhara R, Justice R, Pazdur R. FDA drug approval summary: lapatinib in combination with capecitabine for previously treated metastatic breast cancer that overexpresses HER-2. *Oncologist* 2008; **13**: 1114-1119 [PMID: 18849320 DOI: 10.1634/theoncologist.2008-0816]

99 **Pai SM**, Chaikin P, Berg JK. Pharmacokinetics of Lapatinib, a Nonrenally Cleared Drug, in Patients With End-Stage Renal Disease on Maintenance Hemodialysis. *J Clin Pharmacol* 2019; **59**: 1379-1383 [PMID: 31074516 DOI: 10.1002/jcph.1430]

100 **Guo L**, Shao W, Zhou C, Yang H, Yang L, Cai Q, Wang J, Shi Y, Huang L, Zhang J. Neratinib for HER2-positive breast cancer with an overlooked option. *Mol Med* 2023; **29**: 134 [PMID: 37803271 DOI: 10.1186/s10020-023-00736-0]

101 **Martin M**, Holmes FA, Ejlertsen B, Delaloge S, Moy B, Iwata H, von Minckwitz G, Chia SKL, Mansi J, Barrios CH, Gnant M, Tomašević Z, Denduluri N, Šeparović R, Gokmen E, Bashford A, Ruiz Borrego M, Kim SB, Jakobsen EH, Ciceniene A, Inoue K, Overkamp F, Heijns JB, Armstrong AC, Link JS, Joy AA, Bryce R, Wong A, Moran S, Yao B, Xu F, Auerbach A, Buyse M, Chan A; ExteNET Study Group. Neratinib after trastuzumab-based adjuvant therapy in HER2-positive breast cancer (ExteNET): 5-year analysis of a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol* 2017; **18**: 1688-1700 [PMID: 29146401 DOI: 10.1016/S1470-2045(17)30717-9]

102 **Kidney Disease: Improving Global Outcomes (KDIGO) Transplant Work Group**. KDIGO clinical practice guideline for the care of kidney transplant recipients. *Am J Transplant* 2009; **9** Suppl 3: S1-155 [PMID: 19845597 DOI: 10.1111/j.1600-6143.2009.02834.x]

103 **Schmid P**, Adams S, Rugo HS, Schneeweiss A, Barrios CH, Iwata H, Diéras V, Hegg R, Im SA, Shaw Wright G, Henschel V, Molinero L, Chui SY, Funke R, Husain A, Winer EP, Loi S, Emens LA; IMpassion130 Trial Investigators. Atezolizumab and Nab-Paclitaxel in Advanced Triple-Negative Breast Cancer. *N Engl J Med* 2018; **379**: 2108-2121 [PMID: 30345906 DOI: 10.1056/NEJMoa1809615]

104 **Anayyat U**, Ahad F, Muluh TA, Zaidi SAA, Usmani F, Yang H, Li M, Hassan HA, Wang X. Immunotherapy: Constructive Approach for Breast Cancer Treatment. *Breast Cancer (Dove Med Press)* 2023; **15**: 925-951 [PMID: 38116189 DOI: 10.2147/BCTT.S424624]

105 **Parisi A**, Cortellini A, Cannita K, Bersanelli M, Ficorella C. Safe Administration of anti-PD-L1 Atezolizumab in a Patient with Metastatic Urothelial Cell Carcinoma and End-Stage Renal Disease on Dialysis. *Case Rep Oncol Med* 2019; **2019**: 3452762 [PMID: 30881713 DOI: 10.1155/2019/3452762]

106 **Wang Y**, He H. Prognostic value of soluble programmed cell death ligand-1 in patients with non-small-cell lung cancer: a meta-analysis. *Immunotherapy* 2022; **14**: 945-956 [PMID: 35822688 DOI: 10.2217/imt-2021-0238]

107 **Cortes J**, Cescon DW, Rugo HS, Nowecki Z, Im SA, Yusof MM, Gallardo C, Lipatov O, Barrios CH, Holgado E, Iwata H, Masuda N, Otero MT, Gokmen E, Loi S, Guo Z, Zhao J, Aktan G, Karantza V, Schmid P; KEYNOTE-355 Investigators. Pembrolizumab plus chemotherapy versus placebo plus chemotherapy for previously untreated locally recurrent inoperable or metastatic triple-negative breast cancer (KEYNOTE-355): a randomised, placebo-controlled, double-blind, phase 3 clinical trial. *Lancet* 2020; **396**: 1817-1828 [PMID: 33278935 DOI: 10.1016/S0140-6736(20)32531-9]

108 **Shirali AC**, Perazella MA, Gettinger S. Association of Acute Interstitial Nephritis With Programmed Cell Death 1 Inhibitor Therapy in Lung Cancer Patients. *Am J Kidney Dis* 2016; **68**: 287-291 [PMID: 27113507 DOI: 10.1053/j.ajkd.2016.02.057]

109 **LaFargue CJ**, Dal Molin GZ, Sood AK, Coleman RL. Exploring and comparing adverse events between PARP inhibitors. *Lancet Oncol* 2019; **20**: e15-e28 [PMID: 30614472 DOI: 10.1016/S1470-2045(18)30786-1]

110 **Cortesi L**, Rugo HS, Jackisch C. An Overview of PARP Inhibitors for the Treatment of Breast Cancer. *Target Oncol* 2021; **16**: 255-282 [PMID: 33710534 DOI: 10.1007/s11523-021-00796-4]

111 **Bruin MAC**, Sonke GS, Beijnen JH, Huitema ADR. Pharmacokinetics and Pharmacodynamics of PARP Inhibitors in Oncology. *Clin Pharmacokinet* 2022; **61**: 1649-1675 [PMID: 36219340 DOI: 10.1007/s40262-022-01167-6]

112 **Rolfo C**, de Vos-Geelen J, Isambert N, Molife LR, Schellens JHM, De Grève J, Dirix L, Grundtvig-Sørensen P, Jerusalem G, Leunen K, Mau-Sørensen M, Plummer R, Learoyd M, Bannister W, Fielding A, Ravaud A. Pharmacokinetics and Safety of Olaparib in Patients with Advanced Solid Tumours and Renal Impairment. *Clin Pharmacokinet* 2019; **58**: 1165-1174 [PMID: 30877569 DOI: 10.1007/s40262-019-00754-4]

113 **Bruin MAC**, Korse CM, van Wijnen B, de Jong VMT, Linn SC, van Triest B, Rosing H, Beijnen JH, van den Broek D, Huitema ADR. A real or apparent decrease in glomerular filtration rate in patients using olaparib? *Eur J Clin Pharmacol* 2021; **77**: 179-188 [PMID: 33319340 DOI: 10.1007/s00228-020-03070-0]

114 **Yu Y**, Durairaj C, Shi H, Wang DD. Population Pharmacokinetics of Talazoparib in Patients With Advanced Cancer. *J Clin Pharmacol* 2020; **60**: 218-228 [PMID: 31489639 DOI: 10.1002/jcph.1520]

World Journal of Clinical Oncology

Submit a Manuscript: https://www.f6publishing.com

World J Clin Oncol 2024 June 24; 15(6): 745-754

DOI: 10.5306/wjco.v15.i6.745

ISSN 2218-4333 (online)

ORIGINAL ARTICLE

Retrospective Study

Characteristics and distinct prognostic determinants of individuals with hepatosplenic T-cell lymphoma over the past two decades

Ayrton Bangolo, Pierre Fwelo, Shraboni Dey, Tanni Sethi, Sowmya Sagireddy, Jawaria Chatta, Ashish Goel, Sneha Nagpaul, Eric Pin-Shiuan Chen, Chiranjeeve Saravanan, Sheeja Gangan, Joel Thomas, Sarah Potiguara, Vignesh K Nagesh, Daniel Elias, Charlene Mansour, Prajakta H Ratnaparkhi, Priyanshu Jain, Midhun Mathew, Taylor Porter, Shadiya Sultan, Shailaja Abbisetty, Linh Tran, Megha Chawla, Abraham Lo, Simcha Weissman, Christina Cho

Specialty type: Oncology

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification
Scientific Quality: Grade C
Novelty: Grade C
Creativity or Innovation: Grade C
Scientific Significance: Grade B

P-Reviewer: Huang M, China

Received: February 23, 2024
Revised: May 1, 2024
Accepted: May 21, 2024
Published online: June 24, 2024
Processing time: 121 Days and 18.6 Hours

Ayrton Bangolo, Shraboni Dey, Tanni Sethi, Jawaria Chatta, Ashish Goel, Sneha Nagpaul, Eric Pin-Shiuan Chen, Chiranjeeve Saravanan, Sheeja Gangan, Joel Thomas, Sarah Potiguara, Vignesh K Nagesh, Daniel Elias, Charlene Mansour, Prajakta H Ratnaparkhi, Priyanshu Jain, Midhun Mathew, Taylor Porter, Shadiya Sultan, Shailaja Abbisetty, Linh Tran, Megha Chawla, Simcha Weissman, Department of Internal Medicine, Palisades Medical Center, North Bergen, NJ 07047, United States

Pierre Fwelo, Department of Epidemiology, Human Genetics, and Environmental Sciences, UTHealth School of Public Health, Houston, TX 77030, United States

Sowmya Sagireddy, Abraham Lo, Department of Medicine, Palisades Medical Center, North Bergen, NJ 07047, United States

Christina Cho, Stem Cell Transplantation and Cellular Therapy, John Theurer Cancer Center, Hackensack, NJ 07601, United States

Corresponding author: Ayrton Bangolo, Doctor, MBBS, MD, Doctor, Department of Internal Medicine, Palisades Medical Center, 7600 River Road, North Bergen, NJ 07047, United States. ayrtonbangolo0@gmail.com

Abstract

BACKGROUND

Hepatosplenic T-cell lymphoma (HSTCL) is a rare and aggressive peripheral T-cell lymphoma with historically dismal outcomes, representing less than one percent of non-Hodgkin lymphomas. Given its rarity, the true incidence of HSTCL is unknown and most data have been extrapolated through case reports. To the best of our knowledge, the largest and most up to date study addressing the epidemiology and outcomes of patients with HSTCL in the United States covered a period from 1996 to 2014, with a sample size of 122 patients.

AIM

To paint the most updated epidemiological picture of HSTCL.

METHODS
A total of 186 patients diagnosed with HSTCL, between 2000 and 2017, were ultimately enrolled in our study by retrieving data from the Surveillance, Epidemiology, and End Results database. We analyzed demographics, clinical characteristics, and overall mortality (OM) as well as cancer-specific mortality (CSM) of HSTCL. Variables with a *P* value < 0.01 in the univariate Cox regression were incorporated into the multivariate Cox model to determine the independent prognostic factors, with a hazard ratio of greater than 1 representing adverse prognostic factors.

RESULTS
Male gender was the most represented. HSTCL was most common in middle-aged patients (40-59) and less common in the elderly (80+). Non-Hispanic whites (60.75%) and non-Hispanic blacks (20.97%) were the most represented racial groups. Univariate Cox proportional hazard regression analysis of factors influencing all-cause mortality showed a higher OM among non-Hispanic black patients. CSM was also higher among non-Hispanic blacks and patients with distant metastasis. Multivariate Cox proportional hazard regression analysis of factors affecting CSM revealed higher mortality in patients aged 80 or older and non-Hispanic blacks.

CONCLUSION
Overall, the outlook for this rare malignancy is very grim. In this retrospective cohort study of the United States population, non-Hispanic blacks and the elderly had a higher CSM. This data highlights the need for larger prospective studies to investigate factors associated with worse prognosis in one ethnic group, such as treatment delays, which have been shown to increase mortality in this racial/ethnic group for other cancers.

Key Words: Extra nodal lymphoma; Mortality; Survival; Racial disparity; Age

Core Tip: Hepatosplenic T-cell lymphoma (HSTCL) is an uncommon and highly aggressive form of non-Hodgkin lymphoma that carries a very poor prognosis. Very little is known about the survival outcomes of patients with HSTCL given its rarity. This study will be the most updated and largest study on the survival outcomes of patients with HSTCL. We found that older age and Non-Hispanic black ethnicity are the single most important factors for poor prognosis.

Citation: Bangolo A, Fwelo P, Dey S, Sethi T, Sagireddy S, Chatta J, Goel A, Nagpaul S, Chen EPS, Saravanan C, Gangan S, Thomas J, Potiguara S, Nagesh VK, Elias D, Mansour C, Ratnaparkhi PH, Jain P, Mathew M, Porter T, Sultan S, Abbisetty S, Tran L, Chawla M, Lo A, Weissman S, Cho C. Characteristics and distinct prognostic determinants of individuals with hepatosplenic T-cell lymphoma over the past two decades. *World J Clin Oncol* 2024; 15(6): 745-754
URL: https://www.wjgnet.com/2218-4333/full/v15/i6/745.htm
DOI: https://dx.doi.org/10.5306/wjco.v15.i6.745

INTRODUCTION

Hepatosplenic T-cell lymphoma (HSTCL) is a malignancy derived from T cells expressing the gamma/delta T-cell antigen and more recently alpha/beta antigen that affects mainly the liver and fills the sinusoids, or the red pulp of the spleen[1-3]. The disease is often diagnosed in relatively younger patients with a history of immunodeficiency, autoimmune disease and or the use of immunosuppressive therapy[1]. However, the majority of cases of HSTCL occur de novo. Discontinuation of immunotherapy does not appear to affect tumor progression[1].

Systemic B symptoms (fever, weight loss, night sweats), abdominal discomfort due to hepatosplenomegaly, and clinical features of cytopenia are often present at diagnosis[4]. Hemophagocytic syndrome can be observed with a rapid disease progression[5,6]. Lymph nodes are not often involved, making it difficult to diagnose the malignancy which can mimic infectious etiologies or other malignant disorders. Diagnosis is made in most cases by liver and/or bone marrow biopsy, or splenectomy[7]. Given its rarity and paucity of clinical trials, the treatment is mostly extrapolated from clinical trials of other peripheral T-cell lymphomas[8]. A satisfactory response to induction chemotherapy has been observed, however, most patients tend to relapse[9,10].

Only a few studies have addressed the overall epidemiology of HSTCL[11-13]. However, there is still a paucity of conclusive data and a lack of adequately powered studies properly defining epidemiology characteristics, survival outcomes, and prognostic factors of patients with HSTCL over the past 2 decades. This is especially important with the more recent emergence of hematopoietic stem cell transplants in the management of this fatal malignancy[14,15].

Using a nationally representative and most up to date database available, we evaluated the independent prognostic factors amongst patients with HSTCL, to help fill in the existing gap of literature on the subject. Furthermore, we aimed to establish patient populations that are predisposed to have a poorer prognosis. In our examination of HSTCL, we have

identified a significantly higher cancer-specific mortality (CSM) among non-Hispanic blacks, a finding unprecedented in the existing literature on this disease. This calls for a comprehensive multidisciplinary approach to explore the underlying causes of this disparity in CSM. Our study not only sheds light on these urgent issues but also sets the stage for both retrospective and prospective research aimed at uncovering the mechanisms behind these prognostic differences.

MATERIALS AND METHODS

Study design

A population-based retrospective cohort study of patients with HSTCL was conducted using the Surveillance, Epidemiology, and End Results (SEER) research plus data, 18 registries, Nov 2020 submission database (http://www.seer.cancer.gov). The SEER Program is one of the largest and most authoritative sources of the cancer-related dataset in the United States, which is sponsored by the United States National Cancer Institute. The SEER 18 database collects cancer incidence, patients' clinicopathological features, and survival data from 18 population-based cancer registries and covers nearly 28% of the United States population[16].

Data selection

Inclusion criteria: All patients with HSTCL diagnosed from 2010 to 2017 were selected in our cohort from the SEER database based on: (1) Primary site [c42.2, c22.0]; and (2) histological type [ICD-O-3: 9716,9702). The above-mentioned ICD-9, ICD-10, and/or ICD-0–3 codes were used to extract data regarding these patients from the SEER database. This database is a critical resource for research, particularly for rare cancers like HSTCL, because it aggregates data from diverse demographics and geographical locations across the United States, enhancing the representativeness and generalizability of the findings. The database is updated regularly, ensuring that the data reflect recent diagnostic, treatment, and survival trends.

Exclusion criteria: We excluded patients with an unknown age at diagnosis, race, or stage of HSTCL.

Study variables

Main exposure: All the variables included in this cohort except year of diagnosis were used as main predictors of prognosis.

Outcomes: Overall mortality (OM): Patients who died of any causes at the end of the study were categorized as "yes", and those who did not were categorized as "no". Cancer-specific mortality: Patients who died of HSTCL at the end of the study were categorized as "yes", and those who died of other causes were classified as "no".

Survival months: For OM, survival time was calculated from the date of diagnosis to the date of death, or the date of last follow-up (December 31, 2017) as reported in the SEER registry. For the CSM, survival time was calculated from the date of diagnosis to the date of HSTCL related death, or the date of last follow-up as recorded in the SEER registry.

Sociodemographic and tumor characteristics: Variables such as age at diagnosis, gender, race (White, Black, and others), origin (Non-Hispanic and Hispanic), stage at diagnosis (localized, regional, and distant), geographic residential area, yearly income, marital status, year of diagnosis, surgery and radiation were extracted.

Statistical analysis

Cox proportional hazard regression model is based on the assumption that hazard rates are proportional over time. Variables with value < 0.1 in the univariate Cox regression model were incorporated into the multivariate Cox proportional analysis to determine the independent prognostic factors associated with OM and CSM, with a hazard ratio > 1 representing adverse prognostic factors. All tests were two-sided, with a confidence interval set as 95% and P value < 0.05 deemed statistically significant. All statistical tests were performed by using Software STATA 18.0.

RESULTS

Our study included a total of 186 patients with a primary diagnosis of HSTCL. Table 1 summarizes the baseline characteristics of patients included in our cohort. A male predominance (68.82%) was observed in our cohort. Most patients were diagnosed between the ages of 40- and 59-years-old (36.02%), while non-Hispanic whites (60.75%) and non-Hispanic blacks (20.97) comprised most of the cohort. The most commonly identified demographic features of diagnosed patients included being diagnosed at later stages (69.35%), coming from counties in metropolitan areas of 1 million persons (63.44%), having an annual income of $75000+ (46.24%), and being married (44.09%). Systemic B symptoms were reported by up to 34.41% of patients and cancer directed surgery was performed in up to 37.63% of patients.

A crude analysis of factors associated with OM and CSM among United States patients between 2000 and 2017 is demonstrated in Table 2. Non-Hispanic blacks had the highest OM. non-Hispanic blacks and those diagnosed at a later stage had the highest CSM. Advanced age, marital status, B symptoms or surgery did not affect the OM nor the CSM.

Table 1 Demographic and Clinicopathologic characteristics of United States patients with hepatosplenic T-cell lymphoma between 2000 and 2017

Characteristics	*n*	%
Total	186	100
Gender		
Female	58	31.18
Male	128	68.82
Age at diagnosis, yr		
0-39	63	33.87
40-59	67	36.02
60-79	44	23.66
80+	12	6.45
Race		
Non-Hispanic white	113	60.75
Non-Hispanic black	39	20.97
Hispanic	15	8.06
Other	19	10.22
Tumor stage		
Localized	44	23.66
Regional	13	6.99
Distant	129	69.35
Living area		
Counties in metropolitan areas of 1 million persons	118	63.44
Counties in metropolitan areas of 250000 to 1 million persons	38	20.43
Counties in metropolitan areas of 250000 persons	17	9.14
Nonmetropolitan counties	13	6.99
Income per year		
$ < $55000	22	11.83
$55000-64999	33	17.74
$65000-74999	45	24.19
$75000+	86	46.24
Marital status		
Married	82	44.09
Single/unknown	78	41.94
Divorced/separated	14	7.53
Widowed	12	6.45
Radiation		
No	173	93.01
Yes	13	6.99
Surgery		
No	116	62.37
Yes	70	37.63
B symptoms		

No	122	65.59
Yes	64	34.41
Year of diagnosis		
2000	1	0.54
2001	6	3.23
2002	5	2.69
2003	11	5.91
2004	10	5.38
2005	5	2.69
2006	11	5.91
2007	7	3.76
2008	8	4.30
2009	12	6.45
2010	11	5.91
2011	14	7.53
2012	10	5.38
2013	16	8.60
2014	12	6.45
2015	14	7.53
2016	14	7.53
2017	19	10.22

Table 3 summarizes the results of multivariate cox proportional hazard regression analyses of characteristics influencing OM and CSM of patients with HSTCL diagnosed between 2000 and 2017. Age 80+ and non–Hispanic blacks had the highest CSM. Once again, we found that advanced age, marital status, annual income, tumor stage, B symptoms or surgery did not affect either the OM or the CSM.

DISCUSSION

Non-Hispanic blacks were found to have a higher CSM. To the best of our knowledge, our cohort is the first to make this observation in HSTCL. HSTCL are extremely rare and there is a serious paucity of data in the epidemiologic profile of this malignancy. In this United States population-based study, we found a male and non-Hispanic Whites predominance. Elderly patients were also found to have a worse CSM. Advanced age, marital status, annual income, tumor stage, B symptoms or surgery did not affect the mortality.

Most patients in our cohort were diagnosed between the ages of 40 and 59; these findings are different from the series of Master *et al*[17] where most patients were diagnosed between 25-44 years of age. A male predominance was observed in our cohort which is congruent with the literature[18,19]. Our cohort was predominantly white, findings that also mirror the literature[13].

Splenomegaly is present in all patients with HSTCL[20,21]. The benefits of a splenectomy in the survival of patients with HSTCL remain controversial with conflicting data[21,22]. A single institution observation at mayo clinic did not find any survival benefits of the splenectomy[21], while the study by Gumbs *et al*[22] found substantial benefits of splenectomy especially in patients with severe thrombocytopenia as this intervention led to resolution of the thrombocytopenia and allowed patients to tolerate more aggressive therapies. Up to a third of patients in our cohort underwent a splenectomy. However, this intervention did not seem to affect either OM or CSM.

Most diagnoses of HSTCL were made in metropolitan areas where higher income seemed to correlate with increased incidence compared to lower income. Metropolitan areas tend to be better served with more advanced medical expertise, and given the rarity and nonspecific presentation of HSTCL, patients with higher income will be more likely to afford the extensive medical evaluation required to make the diagnosis.

Systemic B symptoms of fever, night sweats, or weight loss have been reported in 80% of patients with HSTCL[23]. The prognostic value of B symptoms in non-Hodgkin lymphomas remains unclear with opposing data. Studies by Coiffier *et al*[24], and Anderson *et al*[25], found worse prognosis in patients with systemic B symptoms, whereas studies by Portlock *et al*[26], and McLaughlin *et al*[27], were unable to confirm this prognostic value. Up to a third of patients in our cohort had documented systemic B symptoms. However, the systemic B symptoms did not appear to affect OM or CSM.

Table 2 Crude analysis of factors associated with all-cause mortality and hepatosplenic T-cell lymphoma mortality among patients between 2000 and 2017

Characteristics	Overall mortality crude proportional hazard ratio (95% confidence interval)	HSTCL crude proportional hazard ratio (95% confidence interval)
Gender		
Female	1 (reference)	1 (reference)
Male	0.96 (0.65-1.39)	0.99 (0.65-1.52)
Age at diagnosis, yr		
0-39	1 (reference)	1 (reference)
40-59	0.80 (0.53-1.22)	0.69 (0.44-1.11)
60-79	0.95 (0.59-1.54)	0.85 (0.50-1.45)
80+	1.60 (0.68-3.77)	1.44 (0.57-3.65)
Race		
Non-Hispanic white	1 (reference)	1 (reference)
Non-Hispanic black	1.97 (1.27-3.07)[b]	2.34 (1.47-3.72)[b]
Hispanic	1.44 (0.71-2.89)	1.41 (0.64-3.13)
Other	1.65 (0.96-2.86)	1.62 (0.86-3.04)
Tumor stage		
Localized	1 (reference)	1 (reference)
Regional	1.28 (0.57-2.86)	1.63 (0.62-4.30)
Distant	1.54 (0.97-2.43)	2.23 (1.24-4.02)[b]
Living area		
Counties in metropolitan areas of 1 million persons	1 (reference)	1 (reference)
Counties in metropolitan areas of 250000 to 1 million persons	0.73 (0.46-1.16)	0.69 (0.41-1.17)
Counties in metropolitan areas of 250000 persons	1.19 (0.63-2.24)	1.02 (0.49-2.12)
Nonmetropolitan counties	1.43 (0.76-2.70)	1.22 (0.59-2.56)
Income per year		
$ < $55000	1 (reference)	1 (reference)
$55000-64999	1.26 (0.65-2.45)	1.39 (0.65-2.99)
$65000-74999	1.18 (0.63-2.20)	1.25 (0.59-2.61)
$75000+	0.82 (0.45-1.49)	1.02 (0.51-2.03)
Marital status		
Married	1 (reference)	1 (reference)
Single/unknown	1.12 (0.76-1.64)	1.32 (0.86-2.04)
Divorced/separated	1.49 (0.8-2.85)	1.77 (0.88-3.56)
Widowed	1.98 (0.89-4.38)	1.82 (0.72-4.65)
Radiation		
No	1 (reference)	1 (reference)
Yes	0.77 (0.37-1.58)	0.81 (0.38-1.75)
Surgery		
No	1 (reference)	1 (reference)

Yes	0.76 (0.53-1.09)	0.72 (0.48-1.09)
B symptoms		
No	1 (reference)	1 (reference)
Yes	1.23 (0.85-1.80)	1.14 (0.75-1.75)

[b]$P < 0.01$.
HSTCL: Hepatosplenic T-cell lymphoma.

Table 3 Multivariate cox proportional hazard regression analyses of factors affecting all-cause mortality and hepatosplenic T-cell lymphoma related mortality among patients between 2000 and 2017

Characteristics	Overall mortality adjusted proportional hazard ratio (95% confidence interval)	HSTCL adjusted proportional hazard ratio (95% confidence interval)
Gender		
Female	1 (reference)	1 (reference)
Male	0.79 (0.48-1.29)	0.83 (0.49-1.41)
Age at diagnosis, yr		
0-39	1 (reference)	1 (reference)
40-59	0.60 (0.32-1.13)	0.62 (0.30-1.26)
60-79	1.32 (0.67-2.58)	1.65 (0.78-3.49)
80+	2.98 (0.88-10.09)	4.72 (1.14-19.54)[a]
Race		
Non-Hispanic white	1 (reference)	1 (reference)
Non-Hispanic black	1.61 (0.89-2.89)	2.02 (1.08-3.79)[a]
Hispanic	1.87 (0.73-4.78)	1.90 (0.69-5.28)
Other	1.59 (0.79-3.19)	1.49 (0.67-3.37)
Tumor stage		
Localized	1 (reference)	1 (reference)
Regional	0.69 (0.24-2.01)	1.17 (0.33-4.19)
Distant	1.03 (0.57-1.87)	1.85 (0.87-3.89)
Living area		
Counties in metropolitan areas of 1 million persons	1 (reference)	1 (reference)
Counties in metropolitan areas of 250,000 to 1 million persons	1.19 (0.69-2.07)	1.05 (0.55-2.02)
Counties in metropolitan areas of 250000 persons	1.07 (0.44-2.60)	0.68 (0.24-1.94)
Nonmetropolitan counties	2.71 (0.78-9.39)	2.36 (0.50-11.09)
Income per year		
$ < $55000	1 (reference)	1 (reference)
$55000-64999	2.72 (0.82-9.07)	2.54 (0.58-11.08)
$65000-74999	1.75 (0.53-5.85)	1.04 (0.23-4.63)
$75000+	1.46 (0.43-4.96)	1.23 (0.28-5.53)
Marital status		
Married	1 (reference)	1 (reference)
Single/unknown	0.83 (0.48-1.44)	0.94 (0.51-1.75)

Divorced/separated	1.33 (0.61-2.90)	1.79 (0.77-4.19)
Widowed	1.19 (0.39-3.62)	1.01 (0.26-3.87)
Radiation		
No	1 (reference)	1 (reference)
Yes	0.86 (0.35-2.10)	1.07 (0.38-3.01)
Surgery		
No	1 (reference)	1 (reference)
Yes	0.83 (0.49-1.40)	0.97 (0.54-1.76)
B symptoms		
No	1 (reference)	1 (reference)
Yes	1.66 (0.85-3.24)	2.21 (0.99-4.89)

[a]$P < 0.05$.
HSTCL: Hepatosplenic T-cell lymphoma.

Non-Hispanic blacks were found to have a higher CSM. Since the lack of documentation of outcomes in non-Hispanic blacks and given the growth of the Hispanic population in the United States, it is imperative to understand the difference for personalized medicine. Extrapolating data from other cancer areas, several factors have explained higher CSM in non-Hispanic black patients. The study by Fwelo *et al*[28] in breast cancer found that non-Hispanic black women were more likely to undergo treatment delays compared their non-Hispanic White counterparts, and the variations in treatment, socioeconomic status, and clinicopathological factors significantly explained 70% of the excess Breast cancer specific mortality among non-Hispanic Blacks compared to their non-Hispanic White counterparts[29]. A study by Yabe *et al*[6], supported the novel suggestions that HSTCL patients can be stratified into 2 prognostic groups, with an elevated serum bilirubin level, αβ T-cell receptor (TCR) expression, and trisomy 8 correlating with a poorer prognosis. Perhaps most non-Hispanic black patients belong to the group classified by Yabe *et al*[6] as the poorer prognostic group. A multidisciplinary team effort is needed to better understand the reason for this poorer CSM in non-Hispanic Blacks. This study paves the way for future retrospective and prospective studies focusing in part on factors that can potentially explain this variation.

Certain limitations must be considered when interpreting the results of this study. Information gathered on patients that underwent chemotherapy was not complete as the information available was reported as either "yes" or "no/unknown". As a result, that information could not be used in our cohort. Furthermore, the SEER database publicly available does not provide information on comorbidities. However, this study has the merit of collecting data from the largest cancer database in the USA. Furthermore, we were also able to enroll an adequate sample size despite the rarity of the pathology.

CONCLUSION

The elevated CSM rates observed among non-Hispanic Black individuals and older populations over 80 years highlighted in our study bring to the forefront significant disparities in health outcomes. This discrepancy necessitates a deeper investigation into potential causative factors, which may include socioeconomic constraints, unequal access to medical resources, and inherent differences in disease biology. Socioeconomic issues, such as delays in treatment coupled with lower income levels and limited access to high-quality healthcare, can significantly influence survival outcomes across racial lines. Additionally, the accessibility and quality of healthcare services, which vary dramatically with race and age, can affect the timeliness and efficacy of treatment options available to patients. Moreover, biological factors, like distinctive genetic markers and TCR expressions, may also contribute to prognostic differences. These complexities demand a multidisciplinary approach for a fuller understanding and addressing these health inequities. Our study emphasizes the critical need for extensive, targeted research to dissect these multifaceted causes of health disparities, advocating for future studies that not only validate these findings but also examine potential interventions aimed at reducing these disparities. Through such efforts, we can move closer to achieving personalized medicine that caters effectively to the diverse needs of all population segments, thereby improving overall health outcomes.

FOOTNOTES

Author contributions: Bangolo A designed research; Bangolo A, Fwelo P performed research; Bangolo A, Fwelo P, Lo A, Weissman S, Cho C analyzed data; Bangolo A, Fwelo P, Dey S, Sethi T, Sagireddy S, Chatta J, Goel A, Nagpaul S, Chen EPS, Saravanan C, Gangan S, Thomas J, Potiguara S, Nagesh VK, Elias D, Mansour C, Ratnaparkhi PH, Jain P, Mathew M, Porter T, Shadiya Sultan, Abbisetty S, Tran L, Chawla M, Lo A, Weissman S, Cho C wrote the paper.

Institutional review board statement: The SEER Dataset was a public-use dataset, of which the need for IRB approval was waived.

Informed consent statement: The SEER Dataset was a public-use dataset, of which the informed consent was waived.

Conflict-of-interest statement: No potential conflict of interest was reported by the authors.

Data sharing statement: The data used and/or analyzed in this study are available in the Surveillance, Epidemiology, and End Results (SEER) Database of the National Cancer Institute (http://seer.cancer.gov).

Country of origin: United States

ORCID number: Ayrton Bangolo 0000-0002-2133-2480.

S-Editor: Qu XL
L-Editor: A
P-Editor: Zhao YQ

REFERENCES

1 **Tefferi A**, Longo DL. Less Common Lymphoid and Myeloid Malignancies. In: Loscalzo J, Fauci A, Kasper D, Hauser S, Longo D, Jameson JL, editors. Harrison's Principles of Internal Medicine, 21e. NY: McGraw-Hill Education, 2022. Available from: https://accessmedicine.mhmedical.com/content.aspx?bookid=3095&sectionid=265413562

2 **Gaulard P**, Bourquelot P, Kanavaros P, Haioun C, Le Couedic JP, Divine M, Goossens M, Zafrani ES, Farcet JP, Reyes F. Expression of the alpha/beta and gamma/delta T-cell receptors in 57 cases of peripheral T-cell lymphomas. Identification of a subset of gamma/delta T-cell lymphomas. *Am J Pathol* 1990; **137**: 617-628 [PMID: 1698028]

3 **Swerdlow SH**, Campo E, Pileri SA, Harris NL, Stein H, Siebert R, Advani R, Ghielmini M, Salles GA, Zelenetz AD, Jaffe ES. The 2016 revision of the World Health Organization classification of lymphoid neoplasms. *Blood* 2016; **127**: 2375-2390 [PMID: 26980727 DOI: 10.1182/blood-2016-01-643569]

4 **Bron D**, De Leval L, Michiels S, Wittnebel S; EuroBloodNet for rare diseases. Hepatosplenic T-cell lymphoma: treatment challenges. *Curr Opin Oncol* 2021; **33**: 406-411 [PMID: 34409955 DOI: 10.1097/CCO.0000000000000775]

5 **Nosari A**, Oreste PL, Biondi A, Costantini MC, Santoleri L, Intropido L, Muti G, Pungolino E, Gargantini L, Morra E. Hepato-splenic gammadelta T-cell lymphoma: a rare entity mimicking the hemophagocytic syndrome. *Am J Hematol* 1999; **60**: 61-65 [PMID: 9883807 DOI: 10.1002/(sici)1096-8652(199901)60:1<61::aid-ajh10>3.0.co;2-l]

6 **Yabe M**, Medeiros LJ, Tang G, Wang SA, Ahmed S, Nieto Y, Hu S, Bhagat G, Oki Y, Patel KP, Routbort M, Luthra R, Fanale MA, Bueso-Ramos CE, Jorgensen JL, Vega F, Chen W, Hoehn D, Konoplev S, Milton DR, Wistuba I, Li S, You MJ, Young KH, Miranda RN. Prognostic Factors of Hepatosplenic T-cell Lymphoma: Clinicopathologic Study of 28 Cases. *Am J Surg Pathol* 2016; **40**: 676-688 [PMID: 26872013 DOI: 10.1097/PAS.0000000000000614]

7 **Cho MW**, Chin BB. (18)F-FDG PET/CT findings in hepatosplenic Gamma-Delta T-cell lymphoma: case reports and review of the literature. *Am J Nucl Med Mol Imaging* 2018; **8**: 137-142 [PMID: 29755847]

8 **Abouyabis AN**, Shenoy PJ, Sinha R, Flowers CR, Lechowicz MJ. A Systematic Review and Meta-Analysis of Front-line Anthracycline-Based Chemotherapy Regimens for Peripheral T-Cell Lymphoma. *ISRN Hematol* 2011; **2011**: 623924 [PMID: 22084700 DOI: 10.5402/2011/623924]

9 **Garcia-Sanchez F**, Menárguez J, Cristobal E, Cantalejo A, Gil J, Algara P, Vicario JL. Hepatosplenic gamma-delta T-cell malignant lymphoma: report of the first case in childhood, including molecular minimal residual disease follow-up. *Br J Haematol* 1995; **90**: 943-946 [PMID: 7669677 DOI: 10.1111/j.1365-2141.1995.tb05221.x]

10 **Cooke CB**, Krenacs L, Stetler-Stevenson M, Greiner TC, Raffeld M, Kingma DW, Abruzzo L, Frantz C, Kaviani M, Jaffe ES. Hepatosplenic T-cell lymphoma: a distinct clinicopathologic entity of cytotoxic gamma delta T-cell origin. *Blood* 1996; **88**: 4265-4274 [PMID: 8943863 DOI: 10.1182/blood.V88.11.4265.bloodjournal88114265]

11 **Li Y**, Chen K, Zuo C, Zeng R, He Y, Chen X, Xiao L, Zhou H. Survival Analysis of Hepatosplenic T Cell Lymphoma: A Population-Based Study Using SEER. *Int J Gen Med* 2021; **14**: 8399-8411 [PMID: 34819748 DOI: 10.2147/IJGM.S335464]

12 **Dhruvika M**, Radivoyevitch T, Hill BT, Dean RM, Pohlman B, Jagadeesh D. Outcomes in Patients with Enteropathy-Associated T-Cell Lymphoma (EATL) and Hepatosplenic T-Cell Lymphoma (HSTCL): A Population Based Analysis Using the SEER Data. *Blood* 2017; **130**: 2805

13 **Bangolo AI**, Dey S, Mehta R, Jarri AI, Lee SH, Weissman SI, Cho C. Epidemiology and Independent Prognostic Factors of Patients with Hepatosplenic T-Cell Lymphoma over the Past 2 Decades. *Blood* 2023; **142**: 6271-6271 [DOI: 10.1182/blood-2023-185003]

14 **Smith SM**, Burns LJ, van Besien K, Lerademacher J, He W, Fenske TS, Suzuki R, Hsu JW, Schouten HC, Hale GA, Holmberg LA, Sureda A, Freytes CO, Maziarz RT, Inwards DJ, Gale RP, Gross TG, Cairo MS, Costa LJ, Lazarus HM, Wiernik PH, Maharaj D, Laport GG, Montoto S, Hari PN. Hematopoietic cell transplantation for systemic mature T-cell non-Hodgkin lymphoma. *J Clin Oncol* 2013; **31**: 3100-3109 [PMID: 23897963 DOI: 10.1200/JCO.2012.46.0188]

15 **Du J**, Yu D, Han X, Zhu L, Huang Z. Comparison of Allogeneic Stem Cell Transplant and Autologous Stem Cell Transplant in Refractory or Relapsed Peripheral T-Cell Lymphoma: A Systematic Review and Meta-analysis. *JAMA Netw Open* 2021; **4**: e219807 [PMID: 34042995 DOI: 10.1001/jamanetworkopen.2021.9807]

16 **Duggan MA**, Anderson WF, Altekruse S, Penberthy L, Sherman ME. The Surveillance, Epidemiology, and End Results (SEER) Program and Pathology: Toward Strengthening the Critical Relationship. *Am J Surg Pathol* 2016; **40**: e94-e102 [PMID: 27740970 DOI: 10.1097/PAS.0000000000000749]

17 **Master SR**, Koshy NV, Mills GM, Mansour RP, Shi R. Hepatosplenic T-cell lymphoma (HSTL): A SEER data analysis. *J Clin Oncol* 2017; **35**: e19035-e19035 [DOI: 10.1200/JCO.2017.35.15_suppl.e19035]

18 **Durani U**, Go RS. Incidence, clinical findings, and survival of hepatosplenic T-cell lymphoma in the United States. *Am J Hematol* 2017; **92**: E99-E101 [PMID: 28263402 DOI: 10.1002/ajh.24711]

19 **Pro B**, Allen P, Behdad A. Hepatosplenic T-cell lymphoma: a rare but challenging entity. *Blood* 2020; **136**: 2018-2026 [PMID: 32756940 DOI: 10.1182/blood.2019004118]

20 **McKinney M**, Moffitt AB, Gaulard P, Travert M, De Leval L, Nicolae A, Raffeld M, Jaffe ES, Pittaluga S, Xi L, Heavican T, Iqbal J, Belhadj K, Delfau-Larue MH, Fataccioli V, Czader MB, Lossos IS, Chapman-Fredricks JR, Richards KL, Fedoriw Y, Ondrejka SL, Hsi ED, Low L, Weisenburger D, Chan WC, Mehta-Shah N, Horwitz S, Bernal-Mizrachi L, Flowers CR, Beaven AW, Parihar M, Baseggio L, Parrens M, Moreau A, Sujobert P, Pilichowska M, Evens AM, Chadburn A, Au-Yeung RK, Srivastava G, Choi WW, Goodlad JR, Aurer I, Basic-Kinda S, Gascoyne RD, Davis NS, Li G, Zhang J, Rajagopalan D, Reddy A, Love C, Levy S, Zhuang Y, Datta J, Dunson DB, Davé SS. The Genetic Basis of Hepatosplenic T-cell Lymphoma. *Cancer Discov* 2017; **7**: 369-379 [PMID: 28122867 DOI: 10.1158/2159-8290.CD-16-0330]

21 **Bojanini L**, Jiang L, Tun AJ, Ayala E, Menke DM, Hoppe B, Kharfan-Dabaja MA, Tun HW, Alhaj Moustafa M. Outcomes of Hepatosplenic T-Cell Lymphoma: The Mayo Clinic Experience. *Clin Lymphoma Myeloma Leuk* 2021; **21**: 106-112.e1 [PMID: 33160933 DOI: 10.1016/j.clml.2020.09.013]

22 **Gumbs AA**, Zain J, Neylon E, MacGregor-Cortelli B, Patterson M, O'Connor OA. Importance of early splenectomy in patients with hepatosplenic T-cell lymphoma and severe thrombocytopenia. *Ann Surg Oncol* 2009; **16**: 2014-2017 [PMID: 19408055 DOI: 10.1245/s10434-009-0470-0]

23 **Wong KF**, Chan JK, Matutes E, McCarthy K, Ng CS, Chan CH, Ma SK. Hepatosplenic gamma delta T-cell lymphoma. A distinctive aggressive lymphoma type. *Am J Surg Pathol* 1995; **19**: 718-726 [PMID: 7755158 DOI: 10.1097/00000478-199506000-00013]

24 **Coiffier B**, Bosly A, Caligaris-Cappio F, Gisselbrecht C, Patte C, Schaadt M, Symann M. European School of Oncology: management of non-Hodgkin's lymphomas: conclusions of the European School of Oncology Meeting, 1986. *Eur J Cancer Clin Oncol* 1987; **23**: 1691-1695 [PMID: 3322847 DOI: 10.1016/0277-5379(87)90451-2]

25 **Anderson T**, DeVita VT Jr, Simon RM, Berard CW, Canellos GP, Garvin AJ, Young RC. Malignant lymphoma. II Prognostic factors and response to treatment of 473 patients at the National Cancer Institute. *Cancer* 1982; **50**: 2708-2721 [PMID: 7139564 DOI: 10.1002/1097-0142(19821215)50:12<2708::AID-CNCR2820501203>3.0.CO;2-G]

26 **Portlock CS**, Rosenberg SA. No initial therapy for stage III and IV non-Hodgkin's lymphomas of favorable histologic types. *Ann Intern Med* 1979; **90**: 10-13 [PMID: 369420 DOI: 10.7326/0003-4819-90-1-10]

27 **McLaughlin P**, Fuller LM, Velasquez WS, Sullivan-Halley JA, Butler JJ, Cabanillas F. Stage I-II follicular lymphoma. Treatment results for 76 patients. *Cancer* 1986; **58**: 1596-1602 [PMID: 3756784 DOI: 10.1002/1097-0142(19861015)58:8<1596::AID-CNCR2820580803>3.0.CO;2-G]

28 **Fwelo P**, Nwosu KOS, Adekunle TE, Afolayan O, Ahaiwe O, Ojaruega AA, Nagesh VK, Bangolo A. Racial/ethnic and socioeconomic differences in breast cancer surgery performed and delayed treatment: mediating impact on mortality. *Breast Cancer Res Treat* 2023; **199**: 511-531 [PMID: 37052762 DOI: 10.1007/s10549-023-06941-z]

29 **Bangolo A**, Fwelo P, Nwosu KO, Adekunle TE, Afolayan O, Ahaiwe O, Ojaruega AA, Nagesh V, Jarri A, Dey S, Chacko AA, Gupta B, Atoot A. Racial/ethnic and socioeconomic differences in breast cancer surgery performed and delayed surgical treatment: Mediating impact on mortality. *J Clin Oncol* 2023; **41**: 585-585 [DOI: 10.1200/JCO.2023.41.16_suppl.585]

World Journal of Clinical Oncology

Submit a Manuscript: https://www.f6publishing.com

World J Clin Oncol 2024 June 24; 15(6): 755-764

DOI: 10.5306/wjco.v15.i6.755

ISSN 2218-4333 (online)

ORIGINAL ARTICLE

Basic Study

Tankyrase 2 promotes lung cancer cell malignancy

Ying Wang, Yong-Jun Zhang

Specialty type: Oncology

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification

Scientific Quality: Grade A
Novelty: Grade A
Creativity or Innovation: Grade A
Scientific Significance: Grade A

P-Reviewer: Balbaa ME, Egypt

Received: February 25, 2024
Revised: May 9, 2024
Accepted: May 28, 2024
Published online: June 24, 2024
Processing time: 119 Days and 17 Hours

Ying Wang, Department of Gynecological Oncology, Zhejiang Cancer Hospital, Hangzhou 310022, Zhejiang Province, China

Yong-Jun Zhang, Department of Integrated Traditional Chinese and Western Medicine, Zhejiang Cancer Hospital, Hangzhou 310022, Zhejiang Province, China

Corresponding author: Yong-Jun Zhang, MMed, Associate Chief Physician, Department of Integrated Traditional Chinese and Western Medicine, Zhejiang Cancer Hospital, No. 1 Banshan Eastern Road, Hangzhou 310022, Zhejiang Province, China.
zhangyongjun770323@163.com

Abstract

BACKGROUND

Tankyrase 2 (TNKS2) is a potential candidate molecular target for the prognosis and treatment of non-small cell lung cancer (NSCLC), but its biological functions are unclear.

AIM

To investigate the biological functions of TNKS2 in NSCLC.

METHODS

Using a lentiviral vector, we generated H647 model cells with TNKS2 knockdown by RNA interference and A549 model cells with TNKS2 overexpression by transfection with a TNKS2 overexpressing plasmid. Increased and decreased expression levels of TNKS2 in the two cell lines were verified using real-time reverse transcriptase-polymerase chain reaction and Western blot analyses. Cell apoptosis, proliferation, and migration were determined using flow cytometry, carboxyfluorescein succinimidyl ester staining, and scratch assay, respectively. Immunofluorescence staining was conducted to examine TNKS2 and β-catenin expression levels in the two transfected cell lines and the non-transfected cells.

RESULTS

TNKS2 mRNA and protein expression was significantly higher in the highly malignant NCI-H647 cells, while it remained at a low level in the less malignant A549 cells. Lentivirus-mediated overexpression of TNKS2 in A549 cells resulted in a 3-fold increase in gene expression and a 1.7-fold increase in protein expression ($P < 0.01$). Conversely, shRNA interference targeting *TNKS2* Led to an 8-fold decrease in gene expression and a 3-fold decrease in protein expression ($P < 0.01$) in NCI-H647 cells. Furthermore, the cell apoptosis rate was significantly reduced (50%) and cell migration rate was increased (35%) in the TNKS2 overexpression

group than in the control group ($P < 0.05$). In contrast, sh*TNKS2* promoted apoptosis by more than one fold and reduced migration by 60% ($P < 0.05$). Immunofluorescence analysis revealed enhanced nuclear localization of β-catenin fluorescence signal associated with high TNKS2 expression levels. Western blot analysis investigating TNKS2/β-catenin-related proteins indicated consistent changes between TNKS2 and β-catenin expression in lung cancer cells, whereas Axin displayed an opposite trend ($P < 0.05$).

CONCLUSION
The obtained results revealed that TNKS2 may serve as an adverse prognostic factor and a potential therapeutic target in NSCLC.

Key Words: Apoptosis; Migration; Lung Cancer; Proliferation; Tankyrase 2

Core Tip: This study provides a comprehensive overview of the role of tankyrase 2 (TNKS2) overexpression, which facilitates β-catenin activation and nuclear accumulation of β-catenin protein in non-small cell lung cancer (NSCLC) cells, in turn contributing to disease onset and progression. The findings obtained herein elucidate that TNKS2 is a putative molecular target candidate, which would serve as a prognostic indicator and a therapeutic agent for NSCLC patients.

Citation: Wang Y, Zhang YJ. Tankyrase 2 promotes lung cancer cell malignancy. *World J Clin Oncol* 2024; 15(6): 755-764
URL: https://www.wjgnet.com/2218-4333/full/v15/i6/755.htm
DOI: https://dx.doi.org/10.5306/wjco.v15.i6.755

INTRODUCTION

Lung cancer has the highest fatality rate among all cancers worldwide[1,2], and non-small cell lung cancer (NSCLC) is the most common histological subtype, accounting for approximately 85% of all lung cancer cases worldwide[3]. Despite considerable advancements in lung cancer diagnosis and therapy (such as surgery, chemotherapy, and radiation therapy), delays and difficulties in the early diagnosis of NSCLC contribute to its high mortality rates. At first diagnosis, more than 60% of NSCLC cases are at an advanced stage. Consequently, the 5-year survival rate for NSCLC remains less than 20%[4,5]. Non-small-cell lung cancer is a heterogeneous molecular disease. The molecular mechanisms underlying this type of cancer are complex and have not yet been fully elucidated. Currently, a widely accepted pathogenic mechanism of NSCLC is the alteration of gene expression, leading to dysregulation of signaling pathways and abnormal molecular biological behaviors. Therefore, further research on novel molecular markers of NSCLC is required.

Dysregulated β-catenin expression plays a causal role in the pathogenesis of NSCLC[6]. In the canonical activation of the Wnt/β-catenin signal, β-catenin is phosphorylated and degraded, after which it undergoes nuclear translocation and interacts with TCF4/LEF, promoting the transcription of downstream target genes[7]. The poly (ADP-ribose) polymerase (PARP) tankyrase (TNKS) plays a key role in the carcinogenic Wnt/β-catenin signaling pathway, which can not only promote the accumulation of cytoplasmic β-catenin but also participate in the process of driving the transcription of proto-oncogenes[8]. TNKS are a family of enzymes belonging to the PARP superfamily which is located on chromosome 8 and contains 1327 amino acids. TNKS' primary structure includes four domains: The C-terminal catalytic PARP domain that mediates the poly(ADP-ribose) addition to its substrates, a sterile alpha module responsible for the homo- and hetero-oligomer formation, the ankyrin domain divided into five clusters (ARC 1-5) which serve as the substrate binding site, and the His, Pro, and Ser rich domain with unknown function at the N-terminus[9]. TNKS performs various functions in different physiological processes: Mitosis, telomere maintenance, proteasome regulation, GLUT4 vesicles and translocation, viral replication, and Wnt/b-catenin signaling[10].

Expression of the *TNKS2* gene, which is located on 10q23.32, enhances β-catenin activation *via* induction of axin degradation[8]. The Wnt/β-catenin pathway is a promising target for NSCLC[11]. TNKS2 is widely distributed and is involved in the regulation of various physiological and pathological processes, including cell growth[12], signal transduction[13], proliferation and apoptosis[14]. It is also closely associated with the occurrence and development of various diseases, including cancer. However, the expression pattern of TNKS2 in NSCLC cells has not been elucidated. Therefore, in the present study, we explored the underlying mechanism of TNKS2 expression in regulating the biological behavior of NSCLC cells.

MATERIALS AND METHODS

Cell culture

The NSCLC cell lines were purchased from the Cell Bank of the Chinese Academy of Sciences. TNKS2 expression was

high in the H647 cells and low in the A549 cells, as confirmed by real-time reverse transcriptase-polymerase chain reaction (RT-qPCR) and western blot analyses. Briefly, H647 cells were cultured in an RPMI-1640 medium (Corning, Shanghai, China) supplemented with 10% fetal bovine serum (FBS; Gibco, NY, United States). A549 cells were cultured in DMEM (Corning) containing 10% FBS. All the cells were grown in an incubator with saturated humidity at 37 °C and 5% CO_2.

Transfection

A549 and H647 cells were seeded in 12-well plates (Fisher Scientific, United States) at a density of approximately 40%. On day 2 of the culture, H647 cells were infected with the corresponding shRNA (shRNA sequences designed by Invitrogen Life Technologies). The shRNA sequences (Table 1) were designed to target different coding regions of the human *TNKS2* mRNA sequence [GenBank Accession No. NM_025235.3], and A549 cells were infected with a lentivirus for TNKS2 overexpression. After 48 h of infection, the cells were selected with 1 μg/mL of puromycin for 48 h. Transfection efficiency was assessed by quantitative polymerase chain reaction (qPCR) and Western blotting.

RT-qPCR

RNA was extracted from the cells using an RNAiso Plus kit (TaKaRa, 9108). Eppendorf tubes and tips were soaked in 0.1% diethylpyrocarbonate, and the total RNA was digested using DNase I (TaKaRa, 2270A). After determining RNA purity and concentration, it was reverse-transcribed to cDNA using the RevertAid First-Strand cDNA Synthesis Kit (Thermo, K1622). The reverse transcription system included 5 μL total RNA, 4 μL 5 × TransScript All-in-One SuperMix for qPCR, 1 μL gDNA Remover, and 10 μL Rnase-free double-distilled water (ddH_2O). qPCR was performed using the Sso Advance Universal SYBR Green Supermix (Bio-Rad, cat 172-5274). The qPCR reaction system is listed as follows: SybrGreen qPCR Master Mix (2 ×) 10 μL, forward primer (10 uM) 0.4 μL, reverse primer (10 uM) 0.4 μL, ddH20 7.2 μL, and template (cDNA) 2 μL. The primer sequences are shown in Table 1. The PCR conditions were set as follows: 3-min predenaturation at 95 °C, followed by 45 cycles, each consisting of 7-s denaturation at 95 °C, 10-s annealing at 57 °C, and 15-s extension at 72 °C. The relative expression levels were calculated by the $2^{-\Delta\Delta Ct}$ method, using homo *GAPDH* as the internal reference.

Western blot analysis

Cells were lysed in a RIPA buffer (CWBIO, CW2334S) containing protease and phosphatase inhibitors (CWBIO, CW2383S). Protein samples were quantified using a bicinchoninic acid assay protein assay kit (Sigma-Aldrich). Briefly, the protein samples (10 μg) were subjected to 10% SDS-PAGE and transferred onto polyvinylidene fluoride membranes (Bio-Rad). The membranes were blocked with 5% non-fat milk for 1 h at 37 °C. The membranes were then incubated with primary antibodies against TNKS2 (1:1000 dilution; Santa Cruz Biotechnology, sc-365897) or the loading control GAPDH (1:2000; Abcam, ab8245) at 4 °C overnight, before incubation with a secondary goat anti-mouse IgG (1:1000; Biosharp, BL001A). Immunoreactivity was detected using an ECL kit and analyzed using ImageJ software (NIH, United States).

Flow cytometry

An annexin V-APC/7-ADD apoptosis kit (Lianke, 70-AP105-100) was used to detect apoptosis. After the cells in the logarithmic growth phase were trypsinized, they were centrifuged at 500 × *g* for 5 min. The cells were seeded in wells of a six-well plate (8 × 10^4 cells/well) and incubated overnight. On day 2, they were centrifuged at 500 × *g* for 5-10 min at room temperature (22-25 °C) and collected for flow cytometry. After washing twice with 1 × phosphate-buffered saline (PBS; precooled at 4 °C), the cells were centrifuged at 500 × *g* for 5-10 min. They were then resuspended in 1 × binding buffer (diluted with ddH_2O), and the cell density was adjusted to 1 × 10^6-1 × 10^7 cells/mL. Thereafter, 100 μL of the cell suspension was transferred to a flow tube, so that each tube contained approximately 1 × 10^5 to 1 × 10^6 cells. Following this, 5 μL Annexin V-APC and 10 μL 7-ADD were added to each tube, and the mixture was incubated at room temperature for 15 min in darkness. Subsequently, 300 μL of 1 × binding buffer was added to the cells, and they were transferred to a flow tube and tested on a NovoCyte Flow Cytometer (Agilent, United States).

Carboxyfluorescein succinimidyl ester detection of cell proliferation

The cells were resuspended in PBS containing 5% fetal calf serum (FCS) before seeding into the wells of a six-well plate (Thermo, United States) at a density of 1 × 10^7/well. A carboxyfluorescein diacetate succinimidyl ester (CFSE) working solution was prepared by adding 1 μL of 5 mmol/L CFSE solution to 1 mL of PBS containing 10% FCS. Thereafter, 1 mL of the CFSE working solution was added to a tube containing 1 mL of the cell suspension, and the mixture was incubated at 37 °C for 5-10 min. After washing thrice with a complete medium and centrifugation, ice-cold RPMI-1640 medium containing 10% FBS was added to the cells, which were then centrifuged at 500 × *g* for 5 min. Cell proliferation was determined by flow cytometry.

Wound healing assay

Logarithmic-phase cells were centrifuged at 500 × *g* for 5 mi and seeded into the wells of a six-well plate (5 × 10^5/well). After the cells were cultured to 80%-90% confluence, a 10 μL pipette tip was used to make a scratch through the cell layer. After washing with PBS to remove any non-adherent cells, the cells were cultured in a medium containing 5% serum for 24 h. At 0 and 24 h of culture, photographs of the cells (100 ×) were obtained using the Leica Application Suite software, and the scratch distance (width) was recorded. The relative cell migration rate was calculated as follows: Experimental group (scratch distance at 0 h-scratch distance at 24 h)/control group (scratch distance at 0 h-scratch distance at 24 h).

Table 1 Sequences of shRNA and primers for real-time reverse transcriptase-polymerase chain reaction

Sequences of shRNA		RT-qPCR primers	
shNC	5′-GCTCAATCCCGACAGTAGAGT-3′	*TNKS2*	*GAPDH*
sh*TNKS2* #1	5′- GCGGAAAGACGTAGTTGAATA-3′	Forward 5′-GCTGAGCCAACCATCCGAAAT-3′	Forward 5′-GGAGCGAGATCCCTCCAAAAT-3′
sh*TNKS2* #2	5′- GACCCCAATGCTCG AGATAAT-3′	Reverse 5′-ACTTGCGTGGCAGTTGACA-3′	Reverse 5′-GGCTGTTGTCATACTTCTCATGG-3′

RT-qPCR: Real-time reverse transcriptase-polymerase chain reaction.

Immunofluorescence staining

For immunofluorescence analysis, cells were centrifuged at 500 × *g* for 5 min and spread on glass coverslips at a density of approximately 40%. The coverslips were placed in the wells of a 24-well plate. The cells were subjected to immunofluorescence analysis the following day. Briefly, they were fixed with 4% paraformaldehyde for 10 min at room temperature, incubated with 0.2% Triton X-100 solution for 10 min at room temperature, and then blocked with 5% bovine serum albumin solution at 37 °C for 1 h. Thereafter, the cells were incubated with primary antibodies against β-catenin (1:250 dilution; Abcam, ab2365) and TNKS2 (1:100 dilution; Abcam, ab155545) in a humidified box at 4 °C. The following day, the wet box was incubated at room temperature for 30 min and the cells were washed thrice with 1 × PBS. They were then incubated with 100 μL goat anti-rabbit IgG H&L (APC) (Abcam, pre-adsorbed secondary antibody) at 37 °C for 1 h in darkness. The nuclei were counterstained with 4′,6-diamidino-2-phenylindole. The cells were mounted using a mounting tablet containing an anti-quenching agent. Staining results were evaluated using an Eclipse Ti-S fluorescence microscope (Nikon, Japan).

Statistical analysis

All assays were independently repeated at least thrice. The representative results are presented. Data are expressed as the mean ± SD. Comparisons between different groups were performed using Student's *t*-tests or one-way analysis of variance. Statistical significance was set at $P < 0.05$. All the statistical analyses were performed using GraphPad Prism software (version 8.0; GraphPad, Inc., San Diego, CA, United States).

RESULTS

Construction of an H647 cell line stably transfected with TNKS2 shRNA and A549 cell line transfected with a lentiviral vector for TNKS2 overexpression

To study the role of TNKS2 in NSCLC, we first selected H647 cells, which express a high level of TNKS2, to construct a stably transfected TNKS2 interference cell line, and A549 cells, which have a low TNKS2 expression level, to be transfected with a TNKS2-overexpression lentivirus (Figure 1A-C). To avoid the off-target effects of shRNA, two shRNAs were synthesized. RT-qPCR and Western blot analyses revealed that TNKS2 mRNA and protein levels were significantly downregulated after transfection with sh*TNKS2*. Of the two shRNAs examined, a better interference effect was observed for sh*TNKS2*#2. Therefore, sh*TNKS2*#2 was used for H647 cells and shNC was used as a control in the assay. A549 cells were transfected with a TNKS2-overexpression lentiviral vector or empty control vector. The transfected cells were selected using puromycin. RNA and proteins were extracted from the collected cells for subsequent use in RT-qPCR and Western blot analyses, respectively. The results of RT-qPCR and Western blot analyses revealed the successful construction of a stable TNKS2-overexpressing A549 cell line and a TNKS2 interference H647 cell line, as shown by TNKS2 overexpression at the mRNA and protein levels (Figure 1D and E).

Varying expression of TNKS2 does not affect NSCLC cell proliferation

The proliferative capacity of NSCLC cells transfected with sh*TNKS2* and TNKS2-overexpression lentiviral vectors was assessed. Compared to the rate of proliferation seen in control cells, the proliferative ability of H647 cells was the same as that of cells with silenced TNKS2, whereas the proliferative ability of A549 cells with TNKS2 overexpression was the same as that of A549 cells (Figure 2A).

TNKS2 overexpression inhibits apoptosis of NSCLC cells

Using flow cytometry analysis, we investigated the effects of TNKS2 knockdown or overexpression on apoptosis in NSCLC cells. Our results revealed that TNKS2 knockdown led to a significant increase in the apoptosis rate of H647 cells compared to that in the control group. By contrast, TNKS2 overexpression distinctly inhibited the apoptosis of A549 cells compared to that in the control group (Figure 2B). These results indicated that TNKS2 expression is negatively correlated with apoptosis in NSCLC cells.

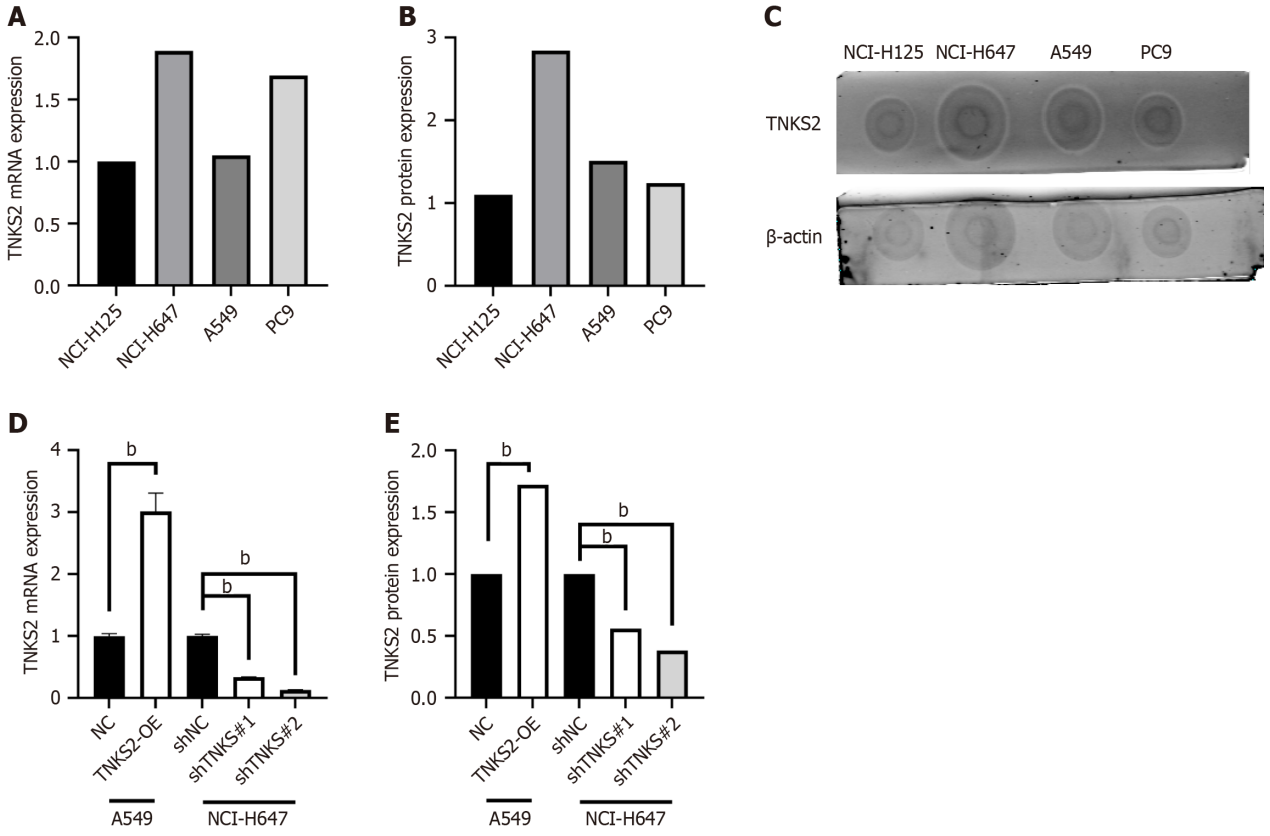


Figure 1 Successful construction of cancer cell lines with TNKS2 knockdown or overexpression. A: Real-time reverse transcriptase-polymerase chain reaction (RT-qPCR) analysis of tankyrase 2 (*TNKS2*) mRNA expression in all four lung cancer cell lines; B and C: Dot-blot analysis of TNKS2 protein expression in all four lung cancer cell lines; D: Construction of stably transfected non-small cell lung cancer cell lines with TNKS2 interference and overexpression. Efficiency of TNKS2 interference or overexpression was assessed in H647 and A549 cells utilizing RT-qPCR; E: Efficiency of TNKS2 interference or overexpression was assessed in H647 and A549 cells *via* Western blot analysis. $^{a}P < 0.05$; $^{b}P < 0.01$.

TNKS2 increases migration ability of NSCLC cells

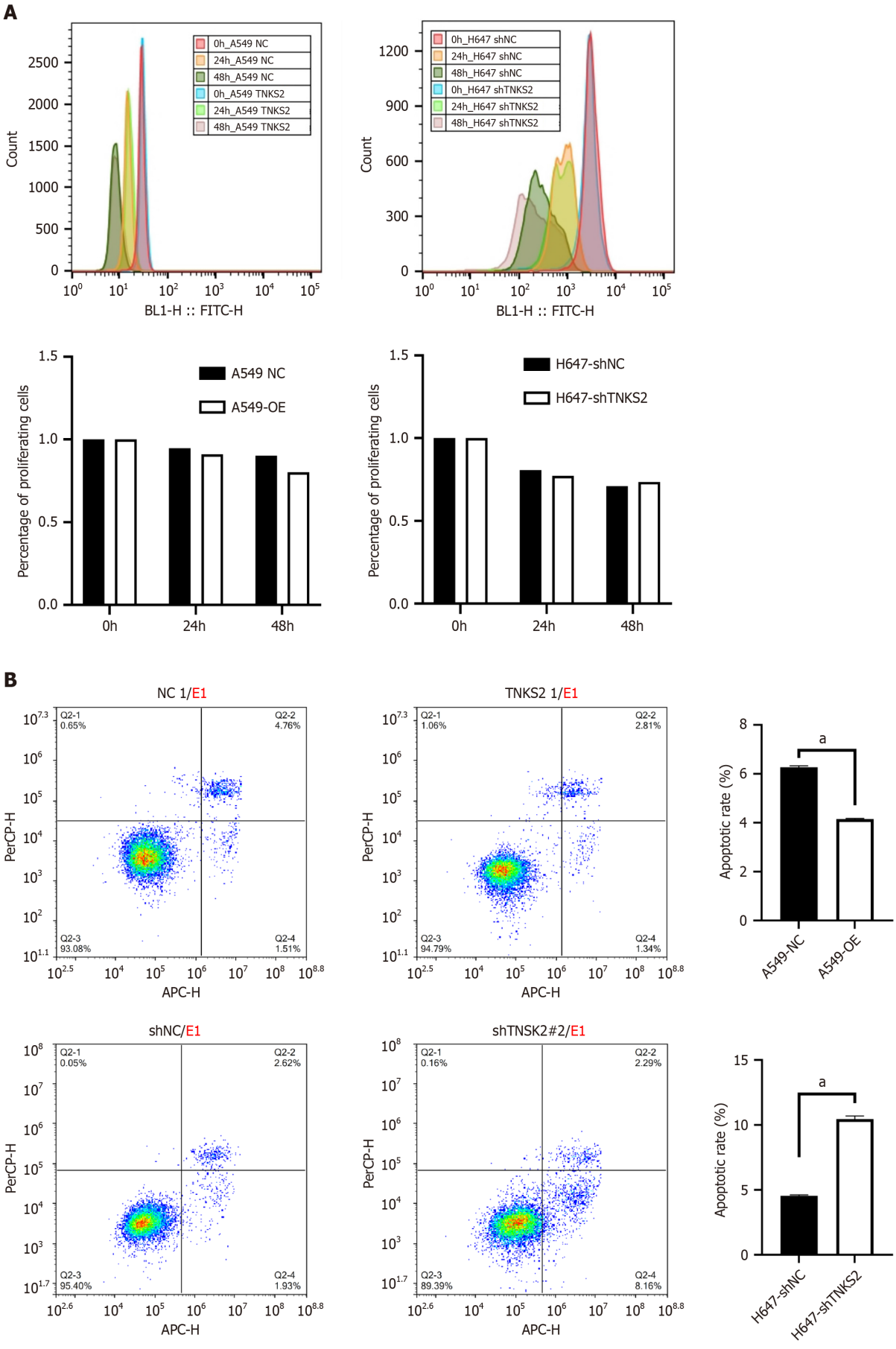
The scratch test was used to determine the influence of TNKS2 silencing or overexpression on the migratory ability of NSCLC cells. Our results showed that TNKS2 knockdown significantly reduced the scratch-healing ability of H647 cells, indicating that cell migration was weakened by TNKS2 knockdown. In contrast, TNKS2 overexpression significantly enhanced the scratch-healing ability of A549 cells, indicating that the migratory ability of A549 cells was enhanced by TNKS2 overexpression (Figure 2C).

TNKS2 overexpression enhances β-catenin signaling activation in NSCLC cells

We used immunofluorescence staining to evaluate the expression of TNKS2 in NSCLC cells transfected with sh*TNKS2* or TNKS2-overexpression vectors. TNKS2 expression notably decreased in sh*TNKS2*-transfected H647 cells. β-catenin protein expression was decreased in both the nucleus and cytoplasm (Figure 3A). Furthermore, immunofluorescence staining was conducted to detect the effects of TNKS2 overexpression on the expression and location of β-catenin. Conversely, its expression was upregulated in A549 cells transfected with a TNKS2-overexpression vector. Upon TNKS2 overexpression, β-catenin protein expression significantly increased in both the nucleus and cytoplasm (Figure 3B). The proteins were then extracted, and the expression of TNKS2/β-catenin-related proteins (axin and β-catenin) was analyzed by Western blotting. β-catenin expression was upregulated with the elevated expression of TNKS2, whereas axin expression was downregulated (Figure 4). These results indicated that TNKS2 overexpression promotes β-catenin activation.

DISCUSSION

Research to discover prognostic markers for NSCLC has attracted increasing attention; however, continued studies are required to identify accurate, simple, and rapid markers for NSCLC[15-17]. Optimal prognostic markers for lung cancer may be determined by conducting studies with rigorous design and large sample sizes. WNT/β-catenin signaling pathway activation has emerged as a potential therapeutic target in NSCLC[18], and there are several candidate therapeutic target proteins in the WNT/β-catenin signaling pathway[19-21]. One study conducted a focused analysis of 500 microarray probes in the Wnt receptor signaling pathway. TNKS1 and *TNKS2* expression levels were 1.30- and 1.43-fold higher in the NSCLC cells than in adjacent normal lung cells in a murine model[22]. In the present study, we


A
0h_A549 NC
24h_A549 NC
48h_A549 NC
0h_A549 TNKS2
24h_A549 TNKS2
48h_A549 TNKS2
Count
BL1-H :: FITC-H
0h_H647 shNC
24h_H647 shNC
48h_H647 shNC
0h_H647 shTNKS2
24h_H647 shTNKS2
48h_H647 shTNKS2
Percentage of proliferating cells
A549 NC
A549-OE
H647-shNC
H647-shTNKS2
0h
24h
48h
B
NC 1/E1
TNKS2 1/E1
shNC/E1
shTNSK2#2/E1
PerCP-H
APC-H
Q2-1 0.65%
Q2-2 4.76%
Q2-3 93.08%
Q2-4 1.51%
Q2-1 1.06%
Q2-2 2.81%
Q2-3 94.79%
Q2-4 1.34%
Q2-1 0.05%
Q2-2 2.62%
Q2-3 95.40%
Q2-4 1.93%
Q2-1 0.16%
Q2-2 2.29%
Q2-3 89.39%
Q2-4 8.16%
Apoptotic rate (%)
a
A549-NC
A549-OE
H647-shNC
H647-shTNKS2

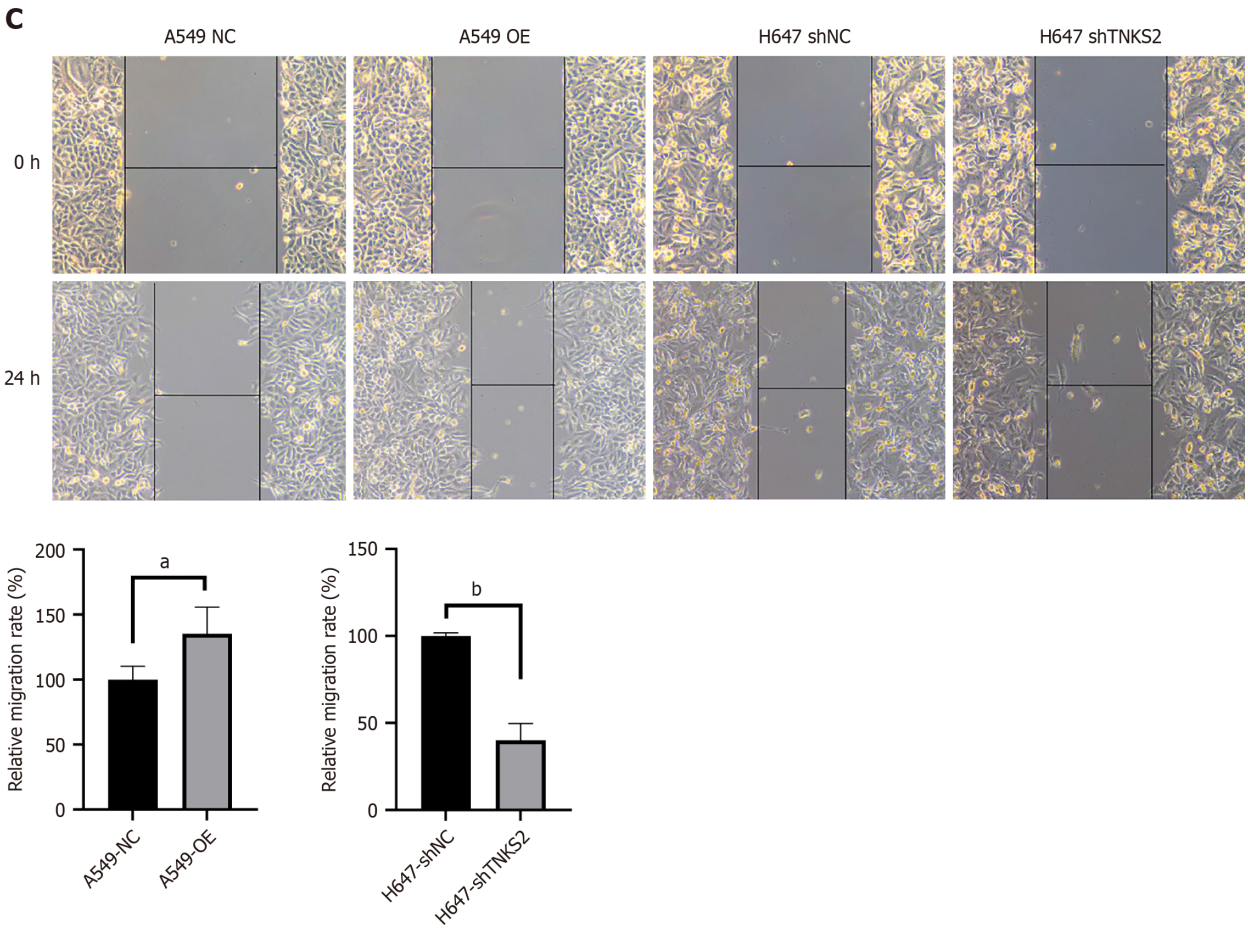


Figure 2 Effects of tankyrase 2 knockdown or overexpression on proliferation of non-small cell lung cancer cells. A: Proliferative ability of H647 cells transfected with sh*TNKS2* and A549 cells with tankyrase 2 (TNKS2) overexpression; B: Apoptosis of non-small cell lung cancer cells assessed by flow cytometry. Apoptotic rate of sh*TNKS2*-transfected H647 cells and TNKS2-overexpressing A549 cells was calculated; C and D: Migration ability of H647 cells transfected with sh*TNKS2* and A549 cells transfected with a TNKS2 overexpression vector at 24 h after transfection (magnification, × 100). $^{a}P < 0.05$; $^{b}P < 0.01$.

provided preliminary evidence to support the hypothesis that TNKS2 overexpression promotes the malignant behavior of lung cancer cells. These results suggest that TNKS2 is a feasible and clinically relevant target for the diagnosis and treatment of NSCLC.

By constructing shRNA and overexpression vectors that alter the expression of TNKS2, we established NSCLC cell lines with stable knockdown or overexpression of TNKS2 and studied the correlation between TNKS2 expression and the biological behavior of NSCLC cells. Low TNKS2 expression led to increased apoptosis in NSCLC cells, while high expression had the opposite effect. Apoptosis is the orderly and autonomous death of cells that is controlled by gene expression to maintain a stable internal environment[23-25]. Unlike cell necrosis, apoptosis is not a passive process but an active one that involves the activation, expression, and regulation of a series of genes. It is not a phenomenon of autologous injury under pathological conditions but a process in which death is induced to actively achieve better adaptation to the living environment. From the perspective of cell apoptosis, tumors occur because of the inhibition of cell apoptotic mechanisms and the inability to clear abnormal cells through apoptosis[26]. Our findings revealed that TNKS2 inhibits apoptosis and induces the proliferation of NSCLC cells.

Malignant tumors easily metastasize through various channels, such as lymphatic vessels and blood circulation[27-29]. Migration and invasion are key processes in tumor metastasis[30-32]. In the present study, we performed a wound-healing assay to determine the effect of TNKS2 on tumor cell migration. Our results revealed that high TNKS2 expression enhanced the migration of NSCLC cells, whereas low TNKS2 expression had the opposite effect. Previous studies have consistently shown that TNKS2 accelerates the growth and invasiveness of triple-negative breast[30] and cervical cancer cells[33]. TNKS2 can dissociate the destruction complex containing axins, thereby enhancing the stability of β-catenin[34]. Activation of β-catenin contributes to the malignant phenotype of NSCLC. Herein, the knockdown and overexpression of TNKS2 inhibited and promoted, respectively, the expression of nuclear β-catenin protein in NSCLC cells, consequently confirming the antitumor potential of inhibiting these molecules in the WNT/β-catenin pathway.

The present study has certain limitations. It only included *in vitro* experiments. As the lungs are the major respiratory organs of the human body, the growth environment and oxygen concentration of lung cancer cells cultured *in vitro* are different from those of lung tissues *in vivo*. Therefore, our results do not reflect the specific effects of TNKS2 on cells *in vivo*. Additionally, future studies need to include a more detailed and in-depth analysis to explore the mechanism of TNKS2/β-catenin or other pathways.

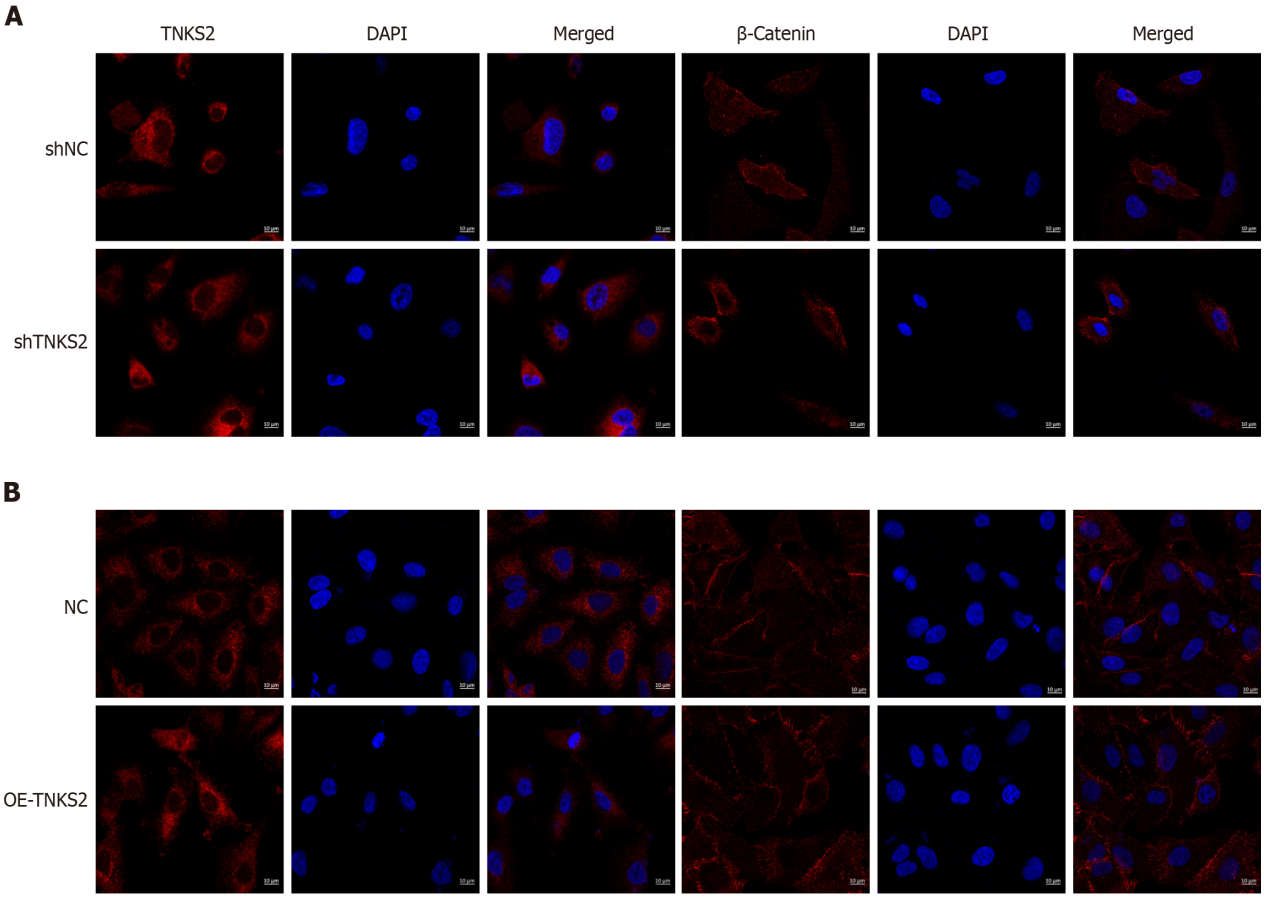


Figure 3 Immunofluorescence images obtained using confocal laser scanning microscopy. A: Tankyrase 2 (TNKS2) and β-catenin expression in sh*TNKS2*-transfected H647 cells; B: TNKS2-overexpressing A549 cells (magnification, × 200). Nuclei were stained blue; the target protein was stained red.

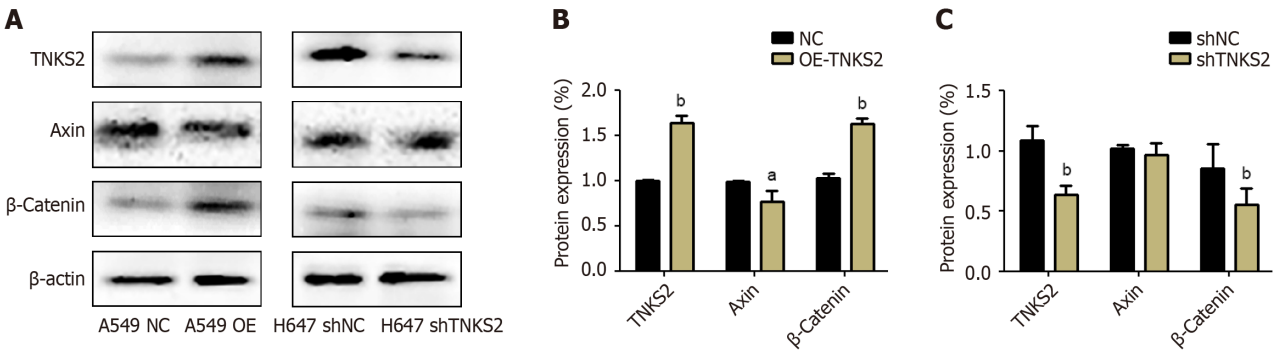


Figure 4 Expression of TNKS2/β-catenin-related proteins assessed by Western blot assay. A: Expression levels of tankyrase 2 (TNKS2), axin, and β-catenin proteins; B: Protein expression of TNKS2-overexpressing A549 cells compared with NC-overexpressing A549 cells was analyzed by gray value; C: Protein expression of sh*TNKS2*-transfected H647 cells compared with shNC H647 cells was analyzed by gray value. $^{a}P < 0.05$; $^{b}P < 0.01$.

The results of the present study provide insights into the biological functions of TNKS2 in NSCLC cells. Furthermore, the obtained findings indicate that TNKS2 may affect the proliferation, apoptosis, and migration of lung cancer cells through the TNKS2/β-catenin pathway. These findings may be useful in the development of therapies targeting TNKS2 for the treatment of NSCLC.

CONCLUSION

Taken together, our results demonstrate that TNKS2 is a promising prognostic factor and therapeutic target for NSCLC. Furthermore, TNKS2 overexpression is associated with the malignant behavior of NSCLC cells (as shown in Figure 5); however, the underlying molecular mechanisms require further investigation.

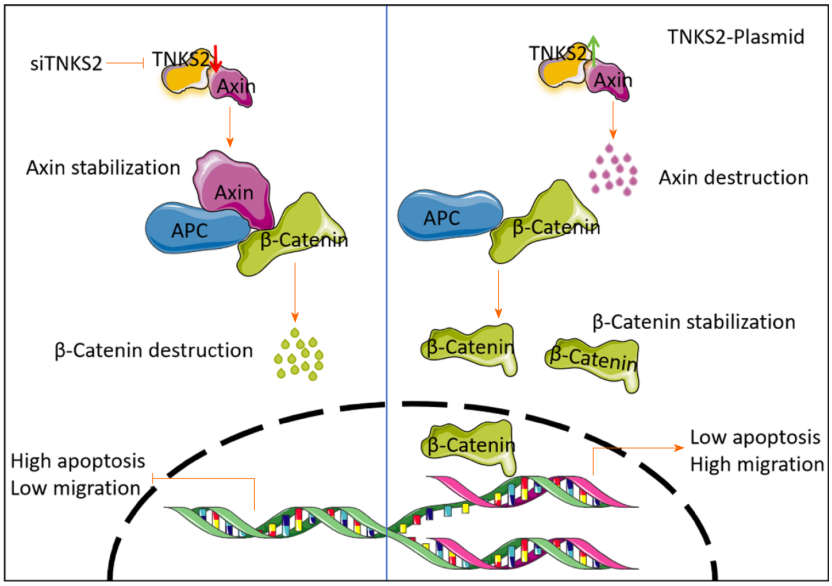


Figure 5 Tankyrase 2 overexpression promotes the malignant behavior of lung cancer cells. Tankyrase 2 dissociates the destruction complex containing axins, thereby enhancing the stability of β-catenin. Activated β-catenin translocates into the nucleus, where it activates target genes, which contribute to the malignant behavior of lung cancer cells.

FOOTNOTES

Author contributions: Wang Y and Zhang YJ designed the research study; Zhang YJ performed the research, analyzed the data, and wrote the manuscript; Wang Y revised the manuscript. All the authors have read and approved the final manuscript.

Supported by Traditional Chinese Medicine Foundation of Zhejiang Province, No. 2019ZA020.

Conflict-of-interest statement: The authors declare no conflicts of interest for this article.

Data sharing statement: Technical appendix, statistical code, and dataset are available from the corresponding author at zhangyongjun770323@163.com.

Country of origin: China

ORCID number: Yong-Jun Zhang 0000-0002-2326-7870.

S-Editor: Qu XL
L-Editor: Wang TQ
P-Editor: Zhao YQ

REFERENCES

1 **Miller KD**, Nogueira L, Devasia T, Mariotto AB, Yabroff KR, Jemal A, Kramer J, Siegel RL. Cancer treatment and survivorship statistics, 2022. *CA Cancer J Clin* 2022; **72**: 409-436 [PMID: 35736631 DOI: 10.3322/caac.21731]
2 **Siegel RL**, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2022. *CA Cancer J Clin* 2022; **72**: 7-33 [PMID: 35020204 DOI: 10.3322/caac.21708]
3 **Herbst RS**, Morgensztern D, Boshoff C. The biology and management of non-small cell lung cancer. *Nature* 2018; **553**: 446-454 [PMID: 29364287 DOI: 10.1038/nature25183]
4 **Zhu X**, Chen L, Liu L, Niu X. EMT-Mediated Acquired EGFR-TKI Resistance in NSCLC: Mechanisms and Strategies. *Front Oncol* 2019; **9**: 1044 [PMID: 31681582 DOI: 10.3389/fonc.2019.01044]
5 **Jin S**, He J, Zhou Y, Wu D, Li J, Gao W. LncRNA FTX activates FOXA2 expression to inhibit non-small-cell lung cancer proliferation and metastasis. *J Cell Mol Med* 2020; **24**: 4839-4849 [PMID: 32176463 DOI: 10.1111/jcmm.15163]
6 **Wang JY**, Wang X, Wang XJ, Zheng BZ, Wang Y, Liang B. Curcumin inhibits the growth *via* Wnt/β-catenin pathway in non-small-cell lung cancer cells. *Eur Rev Med Pharmacol Sci* 2018; **22**: 7492-7499 [PMID: 30468498 DOI: 10.26355/eurrev_201811_16290]

7 **Stewart DJ**. Wnt signaling pathway in non-small cell lung cancer. *J Natl Cancer Inst* 2014; **106**: djt356 [PMID: 24309006 DOI: 10.1093/jnci/djt356]

8 **Mariotti L**, Templeton CM, Ranes M, Paracuellos P, Cronin N, Beuron F, Morris E, Guettler S. Tankyrase Requires SAM Domain-Dependent Polymerization to Support Wnt-β-Catenin Signaling. *Mol Cell* 2016; **63**: 498-513 [PMID: 27494558 DOI: 10.1016/j.molcel.2016.06.019]

9 **Zamudio-Martinez E**, Herrera-Campos AB, Muñoz A, Rodríguez-Vargas JM, Oliver FJ. Tankyrases as modulators of pro-tumoral functions: molecular insights and therapeutic opportunities. *J Exp Clin Cancer Res* 2021; **40**: 144 [PMID: 33910596 DOI: 10.1186/s13046-021-01950-6]

10 **Damale MG**, Pathan SK, Shinde DB, Patil RH, Arote RB, Sangshetti JN. Insights of tankyrases: A novel target for drug discovery. *Eur J Med Chem* 2020; **207**: 112712 [PMID: 32877803 DOI: 10.1016/j.ejmech.2020.112712]

11 **Huang JQ**, Wei FK, Xu XL, Ye SX, Song JW, Ding PK, Zhu J, Li HF, Luo XP, Gong H, Su L, Yang L, Gong LY. SOX9 drives the epithelial-mesenchymal transition in non-small-cell lung cancer through the Wnt/β-catenin pathway. *J Transl Med* 2019; **17**: 143 [PMID: 31060551 DOI: 10.1186/s12967-019-1895-2]

12 **Jia Z**, Liu Y, Gao Q, Han Y, Zhang G, Xu S, Cheng K, Zou W. miR-490-3p inhibits the growth and invasiveness in triple-negative breast cancer by repressing the expression of *TNKS2*. *Gene* 2016; **593**: 41-47 [PMID: 27506313 DOI: 10.1016/j.gene.2016.08.014]

13 **Wang H**, Lu B, Castillo J, Zhang Y, Yang Z, McAllister G, Lindeman A, Reece-Hoyes J, Tallarico J, Russ C, Hoffman G, Xu W, Schirle M, Cong F. Tankyrase Inhibitor Sensitizes Lung Cancer Cells to Endothelial Growth Factor Receptor (EGFR) Inhibition *via* Stabilizing Angiomotins and Inhibiting YAP Signaling. *J Biol Chem* 2016; **291**: 15256-15266 [PMID: 27231341 DOI: 10.1074/jbc.M116.722967]

14 **Lu ML**, Zhang Y, Li J, Fu Y, Li WH, Zhao GF, Li XH, Wei L, Liu GB, Huang H. MicroRNA-124 inhibits colorectal cancer cell proliferation and suppresses tumor growth by interacting with PLCB1 and regulating Wnt/β-catenin signaling pathway. *Eur Rev Med Pharmacol Sci* 2019; **23**: 121-136 [PMID: 30657554 DOI: 10.26355/eurrev_201901_16756]

15 **Bonaventura A**, Grossi F, Montecucco F. PCSK9 is a promising prognostic marker in patients with advanced NSCLC. *Cancer Immunol Immunother* 2020; **69**: 491-492 [PMID: 31938855 DOI: 10.1007/s00262-020-02485-z]

16 **Khandelwal A**, Seam RK, Gupta M, Rana MK, Prakash H, Vasquez KM, Jain A. Circulating microRNA-590-5p functions as a liquid biopsy marker in non-small cell lung cancer. *Cancer Sci* 2020; **111**: 826-839 [PMID: 31520555 DOI: 10.1111/cas.14199]

17 **Wu DM**, Deng SH, Zhou J, Han R, Liu T, Zhang T, Li J, Chen JP, Xu Y. PLEK2 mediates metastasis and vascular invasion *via* the ubiquitin-dependent degradation of SHIP2 in non-small cell lung cancer. *Int J Cancer* 2020; **146**: 2563-2575 [PMID: 31498891 DOI: 10.1002/ijc.32675]

18 **Dai FQ**, Li CR, Fan XQ, Tan L, Wang RT, Jin H. miR-150-5p Inhibits Non-Small-Cell Lung Cancer Metastasis and Recurrence by Targeting HMGA2 and β-Catenin Signaling. *Mol Ther Nucleic Acids* 2019; **16**: 675-685 [PMID: 31121479 DOI: 10.1016/j.omtn.2019.04.017]

19 **He W**, He S, Wang Z, Shen H, Fang W, Zhang Y, Qian W, Lin M, Yuan J, Wang J, Huang W, Wang L, Ke Z. Astrocyte elevated gene-1(AEG-1) induces epithelial-mesenchymal transition in lung cancer through activating Wnt/β-catenin signaling. *BMC Cancer* 2015; **15**: 107 [PMID: 25880337 DOI: 10.1186/s12885-015-1124-1]

20 **Lin S**, Zhen Y, Guan Y, Yi H. Roles of Wnt/β-Catenin Signaling Pathway Regulatory Long Non-Coding RNAs in the Pathogenesis of Non-Small Cell Lung Cancer. *Cancer Manag Res* 2020; **12**: 4181-4191 [PMID: 32581590 DOI: 10.2147/CMAR.S241519]

21 **Xue S**, Wu W, Wang Z, Lu G, Sun J, Jin X, Xie L, Wang X, Tan C, Wang W, Ding X. Corrigendum: USP5 Promotes Metastasis in Non-Small Cell Lung Cancer by Inducing Epithelial-Mesenchymal Transition *via* Wnt/β-Catenin Pathway. *Front Pharmacol* 2020; **11**: 948 [PMID: 32670065 DOI: 10.3389/fphar.2020.00948]

22 **Lim W**, Ridge CA, Nicholson AG, Mirsadraee S. The 8(th) lung cancer TNM classification and clinical staging system: review of the changes and clinical implications. *Quant Imaging Med Surg* 2018; **8**: 709-718 [PMID: 30211037 DOI: 10.21037/qims.2018.08.02]

23 **Guo Y**, Tan J, Miao Y, Sun Z, Zhang Q. Effects of Microvesicles on Cell Apoptosis under Hypoxia. *Oxid Med Cell Longev* 2019; **2019**: 5972152 [PMID: 31178970 DOI: 10.1155/2019/5972152]

24 **Pistritto G**, Trisciuoglio D, Ceci C, Garufi A, D'Orazi G. Apoptosis as anticancer mechanism: function and dysfunction of its modulators and targeted therapeutic strategies. *Aging (Albany NY)* 2016; **8**: 603-619 [PMID: 27019364 DOI: 10.18632/aging.100934]

25 **Xu X**, Lai Y, Hua ZC. Apoptosis and apoptotic body: disease message and therapeutic target potentials. *Biosci Rep* 2019; **39** [PMID: 30530866 DOI: 10.1042/BSR20180992]

26 **Liu G**, Pei F, Yang F, Li L, Amin AD, Liu S, Buchan JR, Cho WC. Role of Autophagy and Apoptosis in Non-Small-Cell Lung Cancer. *Int J Mol Sci* 2017; **18** [PMID: 28208579 DOI: 10.3390/ijms18020367]

27 **Liu Z**, Liang H, Lin J, Cai X, Pan Z, Liu J, Xie X, Li C, Cheng B, Zhao Y, He J, Liang W. The incidence of lymph node metastasis in patients with different oncogenic driver mutations among T1 non-small-cell lung cancer. *Lung Cancer* 2019; **134**: 218-224 [PMID: 31319984 DOI: 10.1016/j.lungcan.2019.06.026]

28 **Yang J**, Peng A, Wang B, Gusdon AM, Sun X, Jiang G, Zhang P. The prognostic impact of lymph node metastasis in patients with non-small cell lung cancer and distant organ metastasis. *Clin Exp Metastasis* 2019; **36**: 457-466 [PMID: 31420766 DOI: 10.1007/s10585-019-09985-y]

29 **Yang XY**, Liao JJ, Xue WR. FMNL1 down-regulation suppresses bone metastasis through reducing TGF-β1 expression in non-small cell lung cancer (NSCLC). *Biomed Pharmacother* 2019; **117**: 109126 [PMID: 31387165 DOI: 10.1016/j.biopha.2019.109126]

30 **Gong R**, Lin W, Gao A, Liu Y, Li J, Sun M, Chen X, Han S, Men C, Sun Y, Liu J. Forkhead box C1 promotes metastasis and invasion of non-small cell lung cancer by binding directly to the lysyl oxidase promoter. *Cancer Sci* 2019; **110**: 3663-3676 [PMID: 31597217 DOI: 10.1111/cas.14213]

31 **He W**, Zhang H, Wang Y, Zhou Y, Luo Y, Cui Y, Jiang N, Jiang W, Wang H, Xu D, Li S, Wang Z, Chen Y, Sun Y, Zhang Y, Tseng HR, Zou X, Wang L, Ke Z. CTHRC1 induces non-small cell lung cancer (NSCLC) invasion through upregulating MMP-7/MMP-9. *BMC Cancer* 2018; **18**: 400 [PMID: 29631554 DOI: 10.1186/s12885-018-4317-6]

32 **Yu M**, Chen Y, Li X, Yang R, Zhang L, Huangfu L, Zheng N, Zhao X, Lv L, Hong Y, Liang H, Shan H. YAP1 contributes to NSCLC invasion and migration by promoting Slug transcription *via* the transcription co-factor TEAD. *Cell Death Dis* 2018; **9**: 464 [PMID: 29700328 DOI: 10.1038/s41419-018-0515-z]

33 **Kang HW**, Wang F, Wei Q, Zhao YF, Liu M, Li X, Tang H. miR-20a promotes migration and invasion by regulating *TNKS2* in human cervical cancer cells. *FEBS Lett* 2012; **586**: 897-904 [PMID: 22449978 DOI: 10.1016/j.febslet.2012.02.020]

34 **Pollock K**, Liu M, Zaleska M, Meniconi M, Pfuhl M, Collins I, Guettler S. Fragment-based screening identifies molecules targeting the substrate-binding ankyrin repeat domains of tankyrase. *Sci Rep* 2019; **9**: 19130 [PMID: 31836723 DOI: 10.1038/s41598-019-55240-5]

World Journal of Clinical Oncology

Submit a Manuscript: https://www.f6publishing.com

World J Clin Oncol 2024 June 24; 15(6): 765-782

DOI: 10.5306/wjco.v15.i6.765

ISSN 2218-4333 (online)

SCIENTOMETRICS

What enlightenment has the development of lung cancer bone metastasis brought in the last 22 years

Yi Chen, Xiao-Song Chen, Rong-Quan He, Zhi-Guang Huang, Hui-Ping Lu, Hong Huang, Da-Ping Yang, Zhong-Qing Tang, Xia Yang, Han-Jie Zhang, Ning Qv, Jin-Liang Kong, Gang Chen

Specialty type: Oncology

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification

Scientific Quality: Grade C, Grade C

Novelty: Grade B, Grade B

Creativity or Innovation: Grade B, Grade B

Scientific Significance: Grade B, Grade B

P-Reviewer: Watanabe T, Japan

Received: February 4, 2024

Revised: May 1, 2024

Accepted: May 22, 2024

Published online: June 24, 2024

Processing time: 141 Days and 6.5 Hours

Yi Chen, Xiao-Song Chen, Zhi-Guang Huang, Hui-Ping Lu, Xia Yang, Han-Jie Zhang, Ning Qv, Gang Chen, Department of Pathology, The First Affiliated Hospital of Guangxi Medical University, Nanning 530021, Guangxi Zhuang Autonomous Region, China

Rong-Quan He, Department of Medical Oncology, The First Affiliated Hospital of Guangxi Medical University, Nanning 530021, Guangxi Zhuang Autonomous Region, China

Hong Huang, Jin-Liang Kong, Department of Respiratory and Critical Care Medicine, The First Affiliated Hospital of Guangxi Medical University, Nanning 530021, Guangxi Zhuang Autonomous Region, China

Da-Ping Yang, Department of Pathology, Guigang People's Hospital of Guangxi/The Eighth Affiliated Hospital of Guangxi Medical University, Guigang 537100, Guangxi Zhuang Autonomous Region, China

Zhong-Qing Tang, Department of Pathology, Wuzhou Gongren Hospital/The Seventh Affiliated Hospital of Guangxi Medical University, Wuzhou 543000, Guangxi Zhuang Autonomous Region, China

Co-first authors: Yi Chen and Xiao-Song Chen.

Co-corresponding authors: Jin-Liang Kong and Gang Chen.

Corresponding author: Gang Chen, MD, PhD, Doctor, Department of Pathology, The First Affiliated Hospital of Guangxi Medical University, No. 6 Shuangyong Road, Nanning 530021, Guangxi Zhuang Autonomous Region, China. chen_gang_triones@163.com

Abstract

BACKGROUND

Lung cancer bone metastasis (LCBM) is a disease with a poor prognosis, high risk and large patient population. Although considerable scientific output has accumulated on LCBM, problems have emerged, such as confusing research structures.

AIM

To organize the research frontiers and body of knowledge of the studies on LCBM from the last 22 years according to their basic research and translation, clinical treatment, and clinical diagnosis to provide a reference for the development of

new LCBM clinical and basic research.

METHODS
We used tools, including R, VOSviewer and CiteSpace software, to measure and visualize the keywords and other metrics of 1903 articles from the Web of Science Core Collection. We also performed enrichment and protein-protein interaction analyses of gene expression datasets from LCBM cases worldwide.

RESULTS
Research on LCBM has received extensive attention from scholars worldwide over the last 20 years. Targeted therapies and immunotherapies have evolved into the mainstream basic and clinical research directions. The basic aspects of drug resistance mechanisms and parathyroid hormone-related protein may provide new ideas for mechanistic study and improvements in LCBM prognosis. The produced molecular map showed that ribosomes and focal adhesion are possible pathways that promote LCBM occurrence.

CONCLUSION
Novel therapies for LCBM face animal testing and drug resistance issues. Future focus should centre on advancing clinical therapies and researching drug resistance mechanisms and ribosome-related pathways.

Key Words: Lung cancer; Bone metastasis; Bibliometrics; Targeted therapy; Immunotherapy; Enrichment analysis

Core Tip: A comprehensive analysis of 1903 publications from 2000 to 2022 was conducted to identify trends in lung cancer bone metastasis (LCBM) research. The literature on LCBM was systematically organized and analysed according to the changing trends in the knowledge volume, distribution of countries/regions, evolution of research topics and co-occurrence of keywords. The results show that immunotherapy and targeted therapy are new research hotspots and ribosome-related genes play an important role in LCBM. This study also preliminarily explored the potential molecular biological mechanisms of LCBM, which mainly involved ribosome and focal adhesion pathways.

Citation: Chen Y, Chen XS, He RQ, Huang ZG, Lu HP, Huang H, Yang DP, Tang ZQ, Yang X, Zhang HJ, Qv N, Kong JL, Chen G. What enlightenment has the development of lung cancer bone metastasis brought in the last 22 years. *World J Clin Oncol* 2024; 15(6): 765-782
URL: https://www.wjgnet.com/2218-4333/full/v15/i6/765.htm
DOI: https://dx.doi.org/10.5306/wjco.v15.i6.765

INTRODUCTION

Currently, lung cancer (LC) bone metastasis (LCBM) is an incurable disease[1]. Patients with LCBM often experience bone and joint pain, pathological fractures and neuropathic pain, which all seriously affect their prognoses and quality of life[2,3]. For many years, LC has had high incidence and mortality rates and the difficulties in early diagnosis mean that many patients have advanced LC at the time of diagnosis[4,5]. The size of the patient population with LCBM is not optimistic as more than 30% of the patients with advanced LC may develop BM[6]. Considering these facts, LCBM can be understood as a life-threatening disease in terms of both the clinical data and symptoms, and it thus requires further study.

Over the past 20 years, a wide range of researchers have gradually started to concentrate on the study of LCBM, and a considerable amount of scientific output has accumulated. However, problems, such as confusing research structures, have arisen. Moreover, no comprehensive or objective metrological studies have been reported on topics such as the tracking or evaluation of the research dynamics of LCBM research. Therefore, while dealing with rapid changes in the study of LCBM, researchers not only face difficulty in quickly grasping these developments, they must also waste additional effort as a result[7,8]. For example, they must also waste additional effort sifting through studies to find relevant data. Bibliometrics, which have the advantage of objectively analysing a large amount of literature on multiple levels, can help solve these problems and have been used extensively in the field of medical research[9].

Therefore, we performed a bibliometric analysis of metrics such as the keywords in articles on LCBM from the Web of Science Core Collection (WOSCC). In addition, we conducted a preliminary investigation of the potential molecular biological mechanisms in LCBM. We hope that this study will help researchers interested in LCBM quickly and accurately grasp the research dynamics involved and provide insights into the global developments in LCBM research.

MATERIALS AND METHODS

Collection of data from articles on LCBM

The data from the articles on LCBM were obtained from the WOSCC (https://www.webofscience.com/). The search formula used in this study was as follows: TS = (("osteolytic metastas*") OR ("metastatic tumor of bone*") OR ("bone metastas*") OR ("osteolytic metastas*") OR ("osteoblastic metastas*") OR ("skeletal metastas*") OR ("bone marrow metastas*") OR ("metastatic carcinoma of bone marrow") OR ("metastatic bone disease")) AND (("lung cancer") OR ("cancer of the lung") OR("cancer of the lung*") OR ("lung *carcinoma") OR ("*carcinoma of the lung*")).

The inclusion and exclusion criteria for the LCBM articles in this study were as follows: (1) To avoid the effects of too many changes in the data due to updates or limitations of the WOSCC, only articles published between 2000 and 2022 were included; (2) To ensure the rigor of the analysis results, only three types of articles were included: Articles, review articles and early-access articles; and (3) Owing to the limitations of the software, only articles written in English were included. In the end, we included 1903 articles (Figure 1).

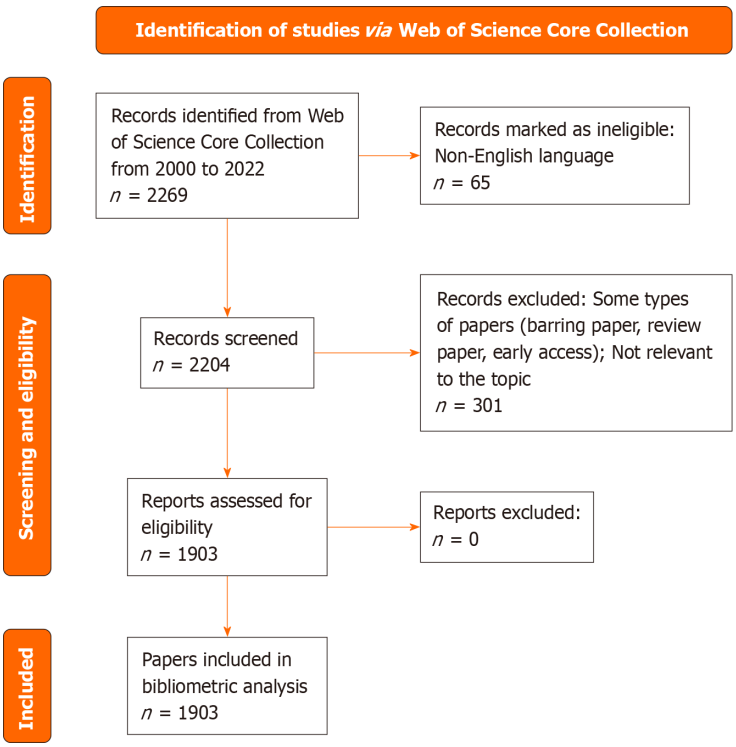


Figure 1 Flowchart of data collection from articles on lung cancer bone metastasis.

All the data for this study were downloaded from the WOSCC in the BibTeX format on January 9, 2023, and the records were "Full Record and Cited Reference". The data collection was performed by two authors. Disagreements between the two authors during this process were discussed in depth and eventually resolved by both authors along with the other authors.

Bibliometric analysis of the data from the articles on LCBM

We used the powerful features of R software (4.2.2), such as advanced statistical calculations, visualization and complete bibliometric analysis, to produce topic evolution maps, keyword time heat maps and other materials. In this study, we also took advantage of VOSviewer software (1.6.18), which can handle large amounts of data and provide strong graphical presentation capabilities for producing keyword clustering maps and other visualisation tools. In addition, we used CiteSpace software (6.1.R6 basic), which can detect hotspot sensitively, and produced keyword burst detection maps.

Exploration of the molecular mechanisms of LCBM

We screened the GSE175601 dataset in the Gene Expression Omnibus, The Cancer Genome Atlas, Sequence Read Archive and ArrayExpress databases based on the criterion that the data should be from *Homo sapiens* tissues with both LC and LCBM tissue data and downloaded the dataset. We then used R software to extract the expression matrix from the dataset and screen the differentially expressed genes (DEGs) of LCBM. The criteria for screening the DEGs were |log fold change| > 1 and P values < 0.05. We then performed Gene Ontology (GO), Kyoto Encyclopedia of Genes and Genomes and Reactome enrichment analyses of the screened DEGs as a preliminary analysis of the potential molecular biological mechanisms of LCBM. In addition, we used STING (v11.5) and Cytoscape (v3.9.1) to construct protein-protein interaction

(PPI) network maps to further analyse the mechanisms involved in LCBM.

RESULTS

Changes in the volume and distribution of knowledge of LCBM

Figure 2A reflects the overall trend of the year-on-year increase in the number of publications and citations since 2000, when 31 papers were published with 10 citations. The volume of knowledge skyrocketed during the last 3 years, with the number of publications exceeding a quarter of the volume of the articles included in this study. The number of citations was no fewer than 10 across 77 articles. Among all of the countries where these articles were published, China had the highest number of publications (602), accounting for approximately one-third of the articles included in this study (Table 1). In addition, other countries that were major contributors to LCBM research include the United States, Japan, and Italy. As shown in Figure 2B and C, developing countries, such as China, Iran, and India, have seen a surge in their number of LCBM-related publications in recent years.

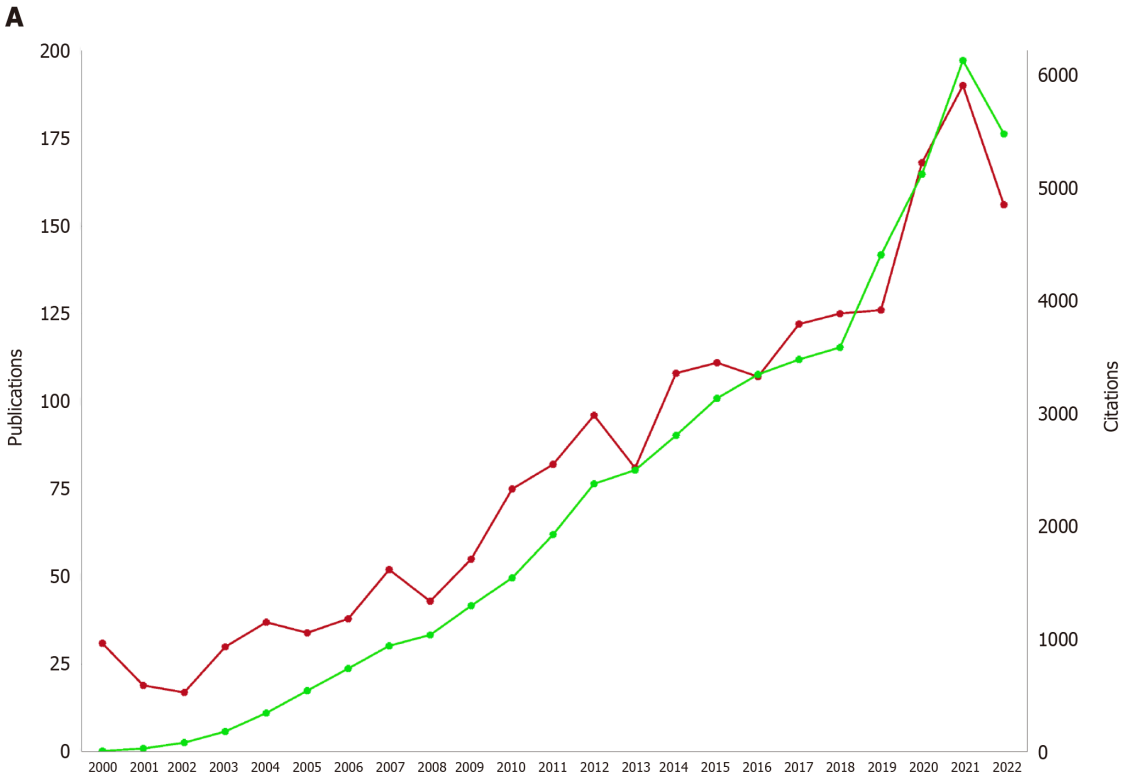
Table 1 Number of articles on lung cancer bone metastasis that were published in countries/regions

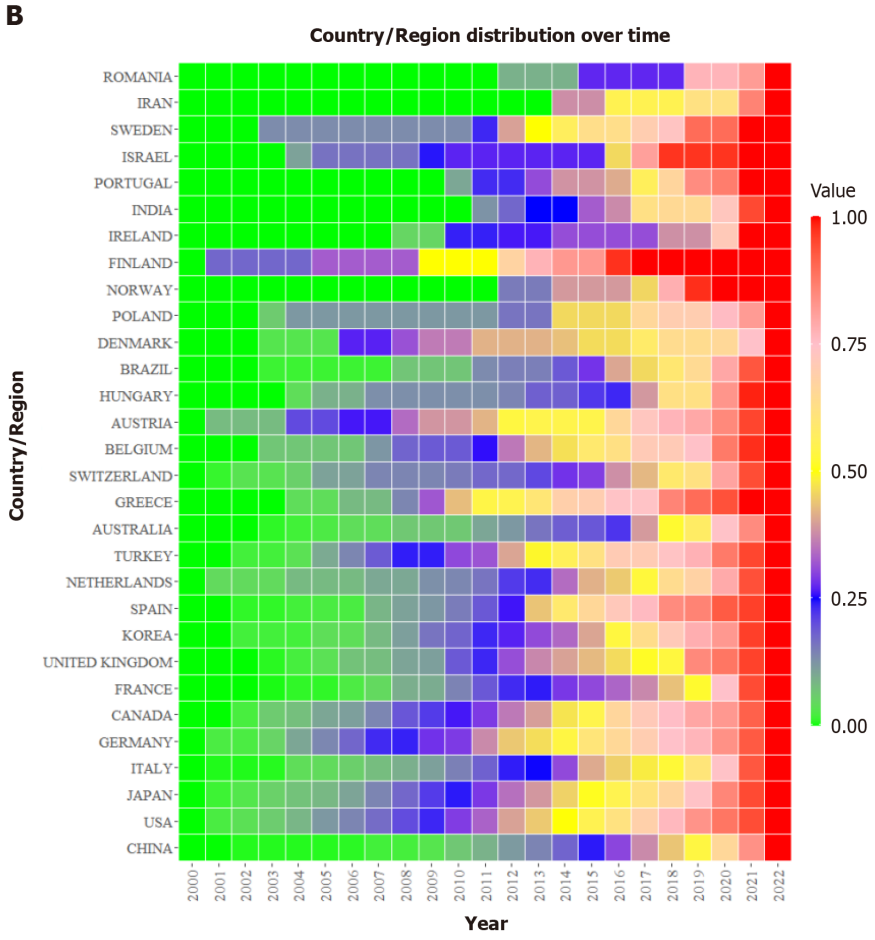
Country/region	Number of publications
China	602
United States	446
Japan	238
Italy	123
Canada	122
Germany	121
United Kingdom	109
Republic of Korea	70
France	68
Spain	60
Netherlands	53
Turkey	46
Australia	42
Switzerland	41
Belgium	33
Austria	32
Greece	31
Brazil	25
Denmark	21
Hungary	16

Thematic changes in LCBM research

Thematic strategic coordinate map for LCBM: We analysed the keywords plus (ID) and authors' keywords (DE) in the LCBM articles (Supplementary Tables 1 and 2, Supplementary Figure 1) and depicted the LCBM hotspot changes using a theme strategy coordinate map (Figure 3). Among the themes identified, zoledronic acid, quality of life and skeletal-related events are the mature and important topics. Palliative, palliative radiotherapy and stereotactic body radiotherapy are mature but currently unimportant topics. Immunotherapy, meta-analysis and epidermal growth factor receptor (EGFR) are immature but important topics, and chemotherapy and docetaxel are marginal topics.

Evolution of the subject terms related to LCBM: We further analysed the changes in the hot topics to capture the knowledge changes in the research on LCBM (Figures 4 and 5). Among the hot topics, immunotherapy, osimertinib, afatinib, EGFR, palliative radiotherapy and SEER have become new focuses of attention, while brain metastasis, lung adenocarcinoma, non-small cell LC and other similar topics have long been the focus of LCBM research.


A
Publications
Citations
0
25
50
75
100
125
150
175
200
0
1000
2000
3000
4000
5000
6000
2000 2001 2002 2003 2004 2005 2006 2007 2008 2009 2010 2011 2012 2013 2014 2015 2016 2017 2018 2019 2020 2021 2022


B
Country/Region distribution over time
Country/Region
ROMANIA
IRAN
SWEDEN
ISRAEL
PORTUGAL
INDIA
IRELAND
FINLAND
NORWAY
POLAND
DENMARK
BRAZIL
HUNGARY
AUSTRIA
BELGIUM
SWITZERLAND
GREECE
AUSTRALIA
TURKEY
NETHERLANDS
SPAIN
KOREA
UNITED KINGDOM
FRANCE
CANADA
GERMANY
ITALY
JAPAN
USA
CHINA
2000 2001 2002 2003 2004 2005 2006 2007 2008 2009 2010 2011 2012 2013 2014 2015 2016 2017 2018 2019 2020 2021 2022
Year
Value
1.00
0.75
0.50
0.25
0.00

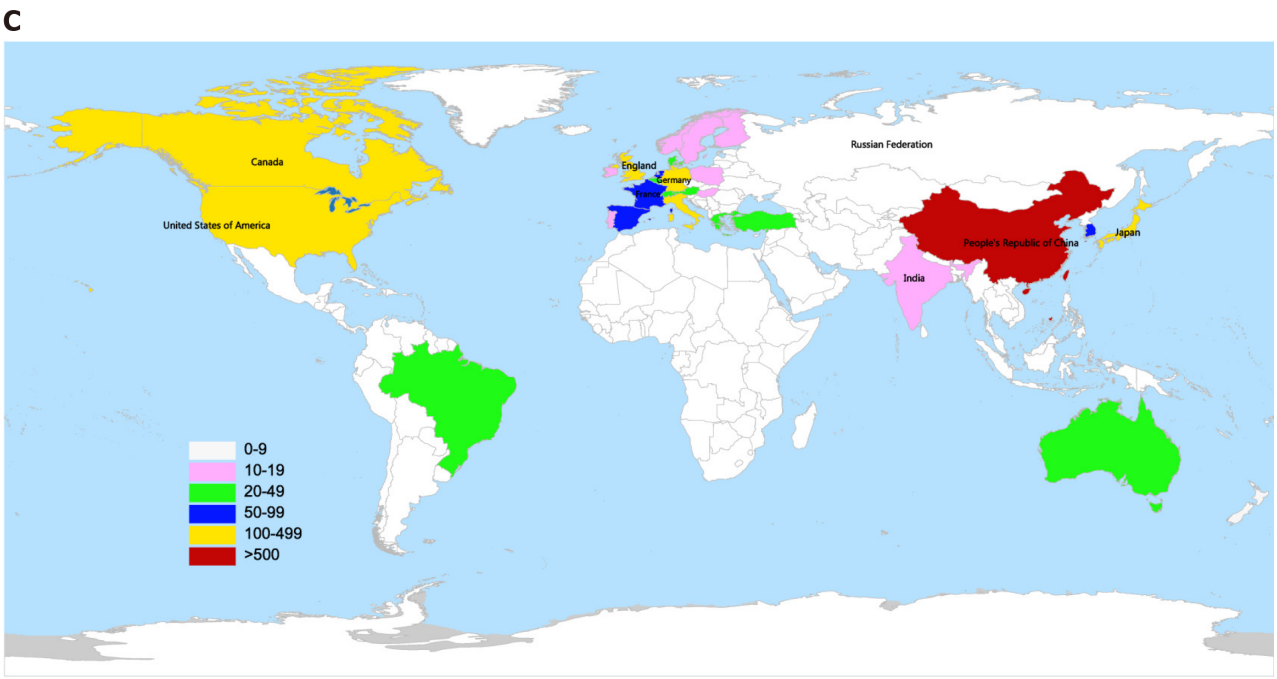


Figure 2 Annual change and distribution map of lung cancer bone metastasis knowledge volume. A: Annual publications and citations of articles on lung cancer bone metastasis (LCBM) from 2000 to 2022, the red line corresponds to "publications"; the green line corresponds to "citations"; B: Thermal diagram of the time distribution of national/regional articles, the values represent the ratio of the total number of papers published in a country from 2000 to a certain year to the total number of papers published in a country; C: Analysis chart of articles on LCBM at the country/region level.

Keyword co-occurrence analysis of articles on LCBM: The construction of an LCBM keyword co-occurrence network is beneficial for an in-depth reproduction of the composition of LCBM knowledge. We extracted 139 high-frequency keywords with over 20 occurrences from 1903 articles for the co-occurrence network construction. The network can be divided into five categories (Figure 6): Cluster 1, basic research (red), including resorption, hormone-related protein, microenvironment and osteoclastogenesis; cluster 2, clinical treatment and related experiments (green), including gefitinib, immunotherapy and chemotherapy, where keywords on immunotherapy and targeted therapy are emerging; cluster 3, clinical diagnostic-related studies (blue), including diagnosis, positron emission tomography (PET) and fluorine-18-fluorodeoxyglucose PET/computed tomography (PET/CT); cluster 4, adjuvant therapy (yellow), including skeletal-related events, zoledronic acid and denosumab; and cluster 5, palliative care (purple), including painful BM and palliative radiotherapy. In addition, we found that some mechanisms, such as EGFR mutation, microRNA and tyrosine kinase inhibitors, were explored and distributed across the clusters.

Exploration of the molecular biological mechanisms of LCBM

We screened 1238 DEGs from the dataset, including 606 upregulated genes and 632 downregulated genes. GO and Reactome functional annotations revealed that the functions of the DEGs in LCBM are mainly focused on the ribosome, the cytosolic ribosome, the formation of the pool of free 40S subunits related to ribosome-related pathways and focal adhesion related to cell adhesion migration (Figure 7). A PPI analysis of the ribosome-related DEGs in LCBM revealed that this pathway is mainly an interaction between the 60S ribosomal protein large subunit (RPL) and 40S ribosomal protein small subunit (RPS) families.

DISCUSSION

BM from primary tumours often suggest a poor prognosis[3,10]. Researchers have long been devoted to studying the basis and mechanisms of LCBM. With the development of high-throughput sequencing, this body of knowledge has exploded. This study is the first to organize and quantify the current large and confusing knowledge structure to provide suggestions for further LCBM research.

Changes in LCBM knowledge volume and country/region distribution

More systematic and precise treatments with immunotherapy and targeted therapy have helped to improve significantly the prognosis in LC, but BM remains a critical problem in these patients[11]. The worldwide LC patient population is very large[12]. In addition, approximately 350000 deaths are caused by BM in the United States each year[13]. This has objectively driven scholars to explore and develop the study of LCBM. The major contributors to LCBM research are primarily in developed countries, reflecting the level of social development needed to promote science and technology.

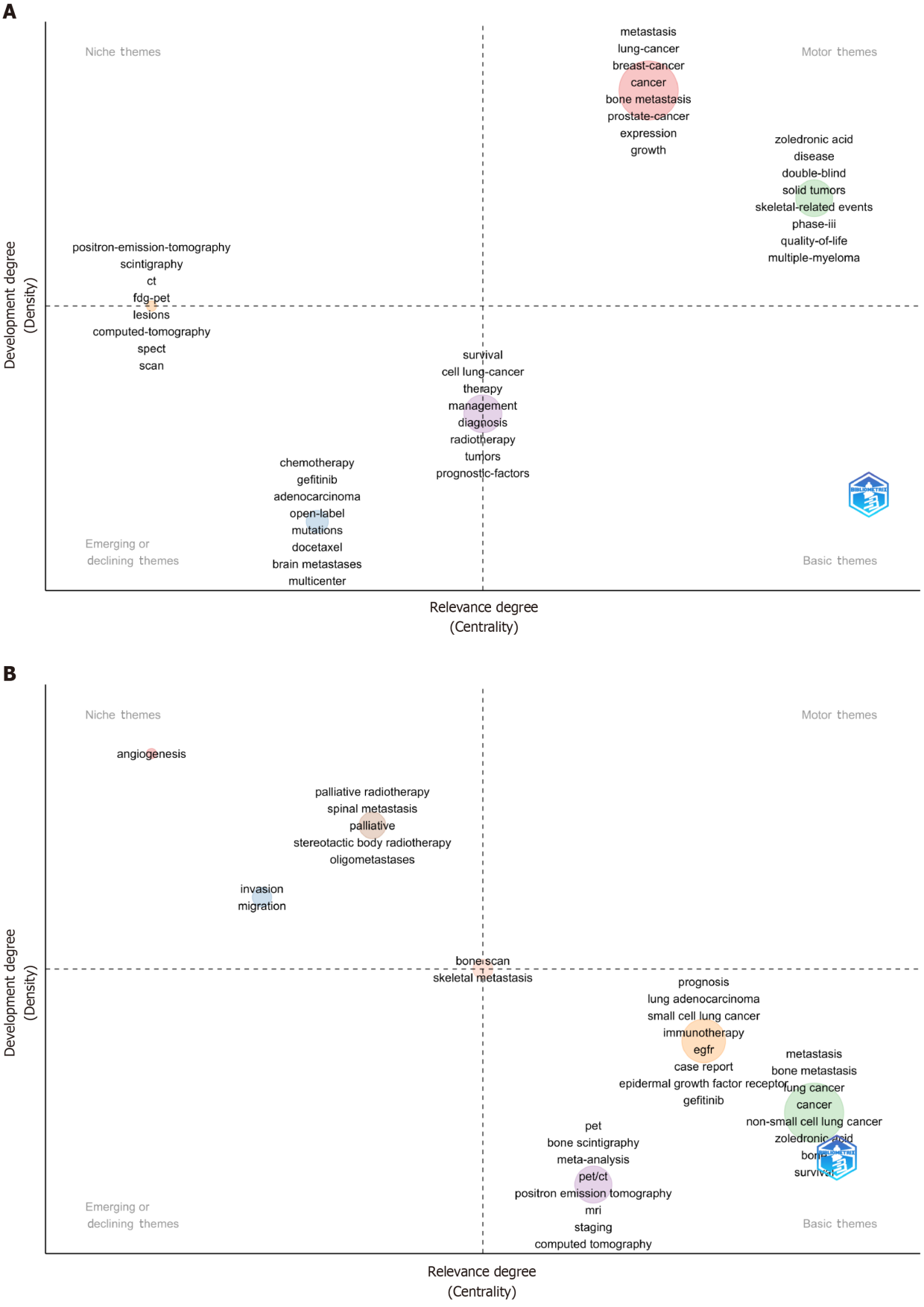


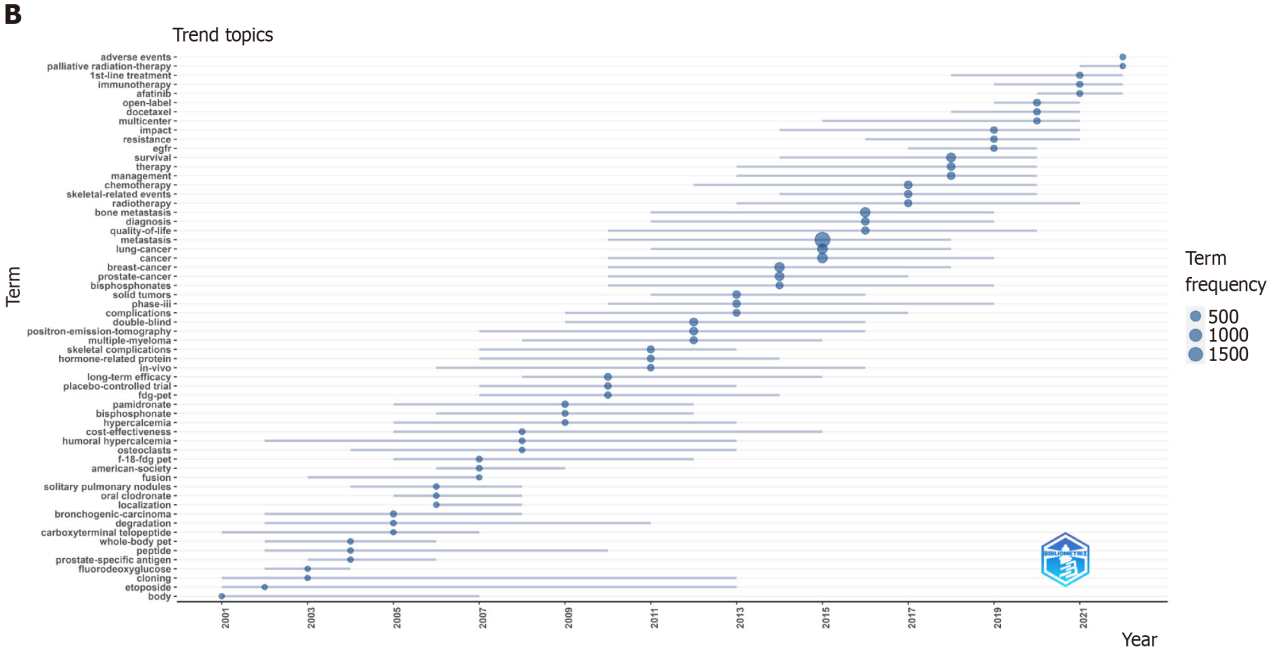
Figure 3 Theme strategic coordinate map. A: Keywords plus; B: Authors' keywords.

A

Top 25 keywords with the strongest citation bursts

Keywords	Year	Strength	Begin	End	2000-2022
positron emission tomography	2000	11.2	**2001**	2009	
multiple myeloma	2002	11.68	**2002**	2012	
fdg pet	2003	8.97	**2003**	2010	
pamidronate	2003	7.84	**2003**	2013	
cell lung cancer	2003	5.43	**2003**	2007	
skeletal complication	2005	14.38	**2005**	2013	
placebo controlled trial	2005	8.59	**2005**	2013	
hormone related protein	2000	7.23	**2005**	2011	
long term efficacy	2006	10.04	**2006**	2013	
bisphosphonate	2003	6.33	**2006**	2011	
breast cancer patient	2006	5.55	**2006**	2010	
phase iii	2005	7.16	**2008**	2013	
scan	2008	6.21	**2008**	2012	
prostate cancer	2000	5.86	**2008**	2011	
solid tumor	2007	10.43	**2009**	2013	
gefitinib	2010	8.33	**2016**	2017	
adenocarcinoma	2000	6.19	**2016**	2017	
lung adenocarcinoma	2014	7.37	**2018**	2022	
docetaxel	2008	6.86	**2018**	2022	
open label	2013	11.67	**2019**	2022	
nivolumab	2018	7.83	**2019**	2022	
immune checkpoint inhibitor	2018	7.66	**2020**	2022	
1st line treatment	2017	6.93	**2020**	2022	
multicenter	2012	6.48	**2020**	2022	
pembrolizumab	2020	5.87	**2020**	2022	

B



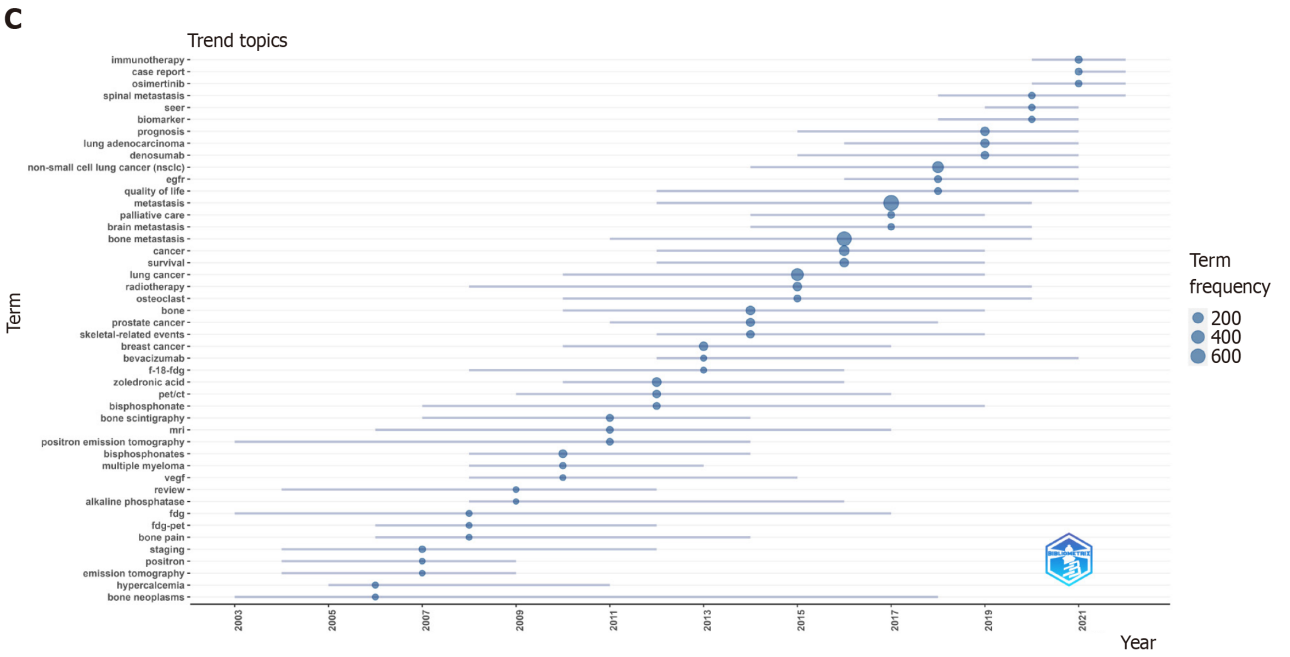


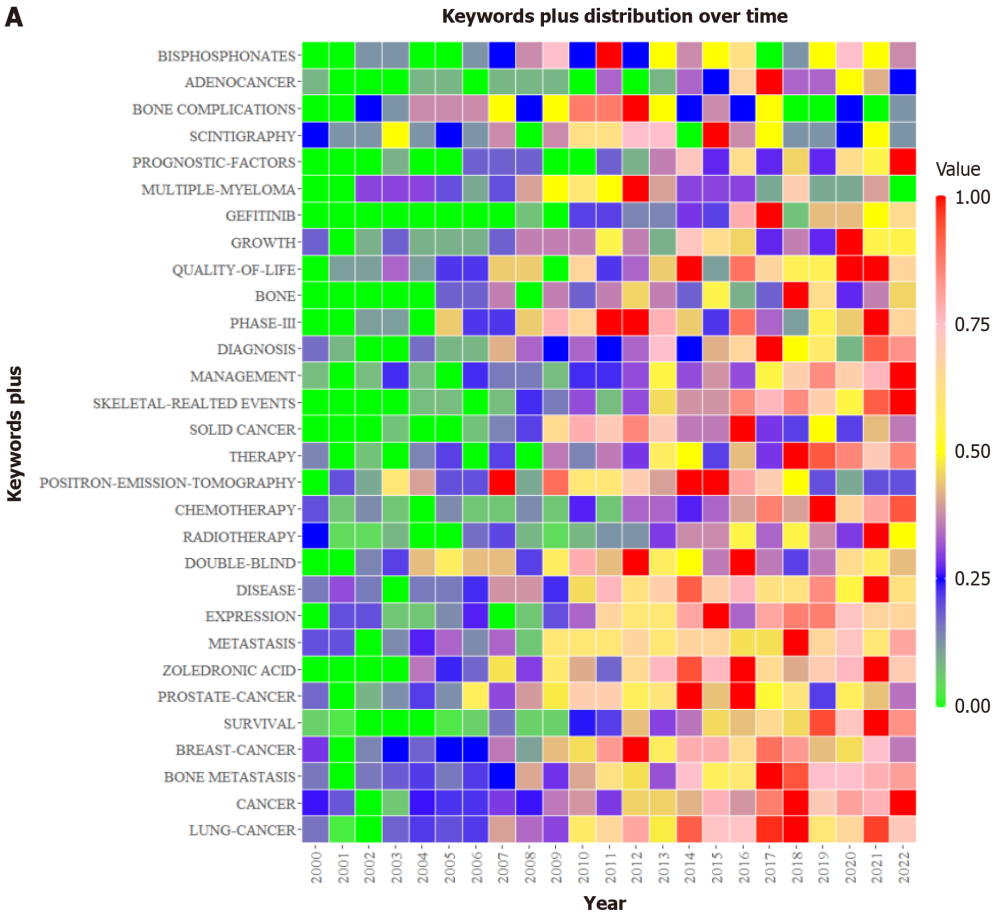
Figure 4 Time distribution chart of popular keywords. A: Burst detection graph of all keywords in articles on lung cancer bone metastasis (LCBM); B: Topic trend graph drawn based on keywords plus of the articles on LCBM; C: Topic trend graph drawn based on the authors' keywords in the articles on LCBM.

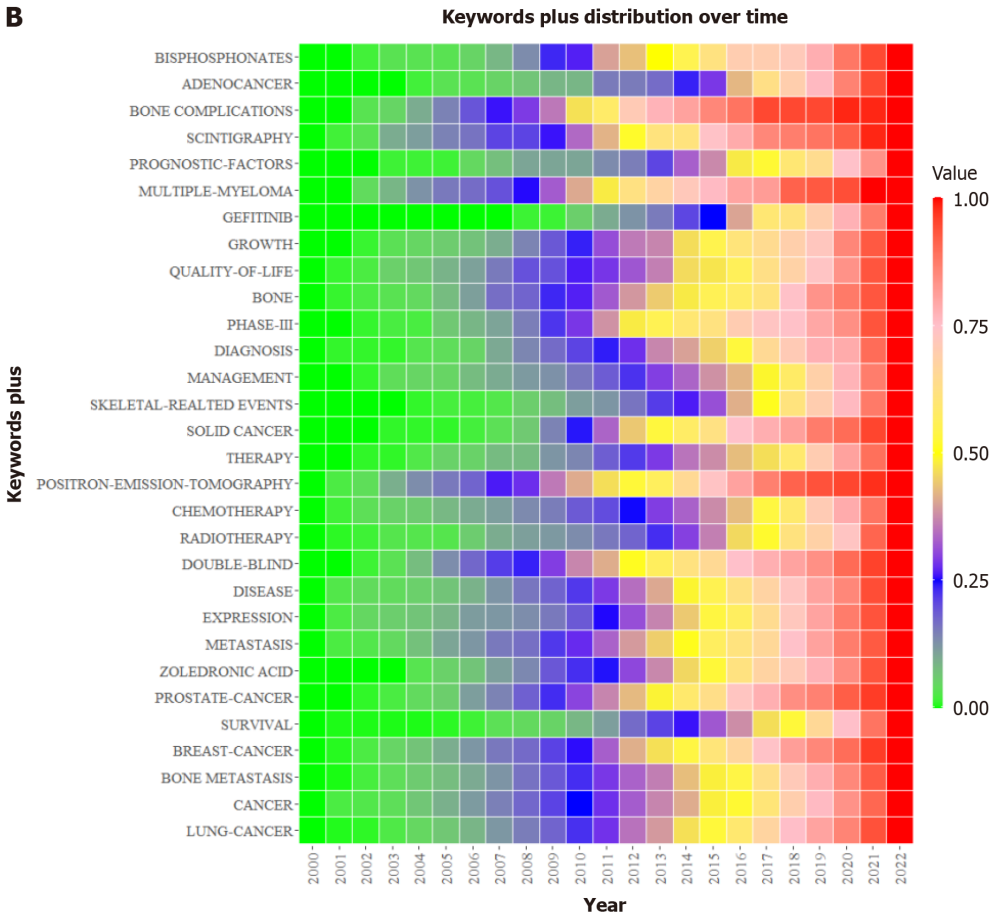
However, some developing countries have emerged in recent years as forces that play an important role in this research. This is helpful for alleviating the dilemma facing developing countries of backward medical technology amid high morbidity and mortality rates for LCBM[12]. Furthermore, developed countries should strengthen their future cooperation efforts with developing countries to help resolve this dilemma (Supplementary Figure 2).

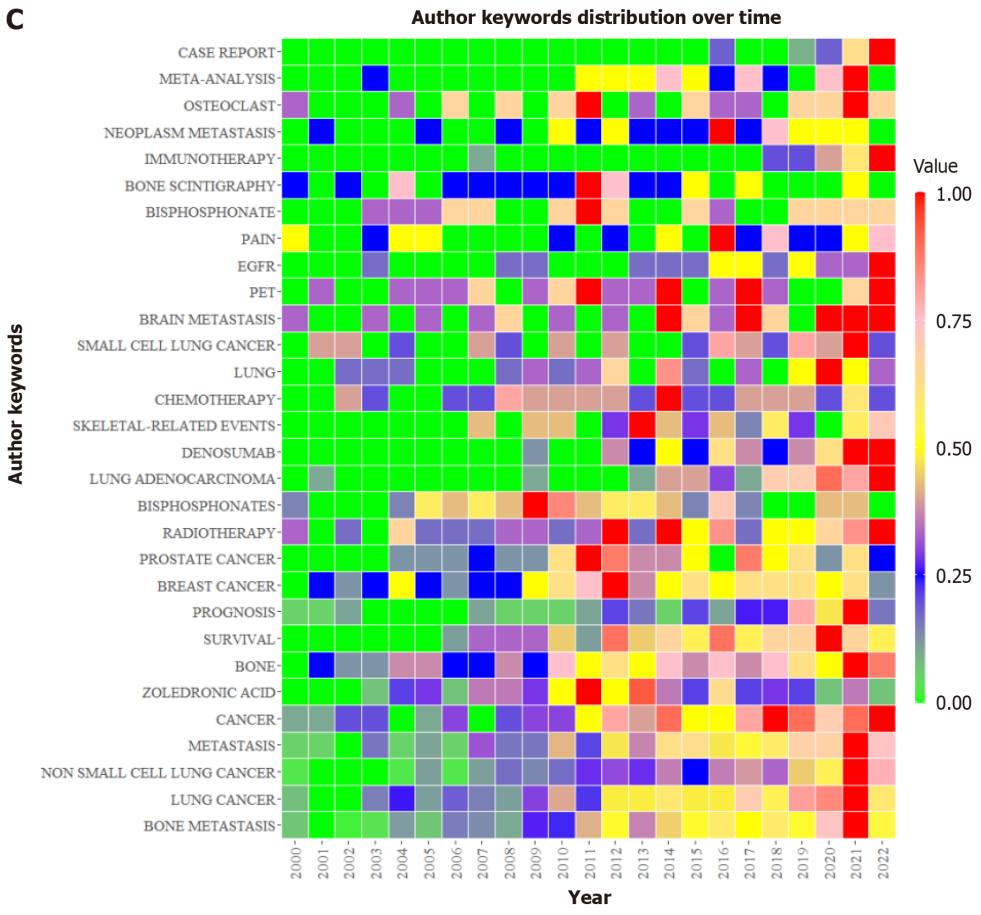
Changes in LCBM research hotspots

At the same time, the development of the knowledge on LCBM has been iterated owing to the continuous exploration and attention of researchers worldwide. Zoledronic acid, quality of life and skeletal-related events constitute the motor themes, suggesting that although neither denosumab nor zoledronic acid can change the outcomes and side effects of patients with LCBM, they can effectively reduce the skeletal-related events associated with a poor prognosis[14,15]. Palliative, palliative radiotherapy and chemotherapy constitute a falling theme that may be related to their relatively limited scope of action, high toxicity, myelosuppression and low efficacy[16,17]. On the other hand, the emergence of targeted therapies is related to the large amount of basic research on EGFR. A previous study claimed that EGFR is mutated in approximately 70% of patients with LCBM[18]. Specifically, in LCBM cells, epidermal growth factor or Wnt signalling pathways stimulate high ROR1 expression levels to interact with EGFR, which in turn promotes cancer cell proliferation, survival and invasion[19]. In addition, acquired resistance generated by first- and second-generation EGFR-tyrosine kinase inhibitors is closely associated with the behaviour of genes, such as the T790M mutation, MET amplification, AXL activation, IGF1R blockade, HER2 amplification, PTEN deletion and PIK3CA mutation[20]. These results invariably drive the creation of more effective EGFR-targeted therapies. The clinical application of immunotherapy is dependent on the maturation of research on immune mechanisms and the promotion of immune checkpoint inhibitors[21]. These are also examples of the basic research that drives clinical progress. Therefore, it is necessary to strengthen the basic research in the future to improve and clarify the relevant molecular mechanisms in LCBM. In recent years, the maturation of computer and other technologies, such as high-throughput sequencing, has enabled bioinformatics to become widely used in the study of LCBM. For example, *in vitro* models of LC cell-derived exocysts have been constructed to predict their BM capacity using methods such as meta-analysis[22]. Using meta-analyses, Sharma *et al* [23] and Chen *et al*[24] evaluated the efficacy of brachytherapy as compared with denosumab and zoledronic acid therapies in patients with LCBM. In an analysis of data from 8067 patients with advanced NSCLC, the use of programmed cell death protein 1 inhibitors in patients with BM was found to have no significant altering effect on progression-free survival[25]. In addition, the log-rank test, multiple Cox regression analysis and Kaplan-Meier method are other common research tools[26]. These studies are important for research on the construction of prognostic models, assessment of clinical outcomes and development of molecular diagnoses and treatments. This suggests that bioinformatic analysis may presently be an effective method for studying LCBM; however, most studies still lack further experimental validation.

In addition, as long-standing topics of interest in the field of LCBM, lung adenocarcinoma, non-small cell LC and so on reflect the large patient base of non-small cell LC, which is the most common type of LC[12,27]. However, brain and other metastases have also emerged as themes as they share some common problems. For example, both BM and brain metastasis in LC are closely related to the interaction of various components of the LC microenvironment, such as the epithelial-mesenchymal transition[28,29].


A
Keywords plus distribution over time
BISPHOSPHONATES
ADENOCANCER
BONE COMPLICATIONS
SCINTIGRAPHY
PROGNOSTIC-FACTORS
MULTIPLE-MYELOMA
GEFITINIB
GROWTH
QUALITY-OF-LIFE
BONE
PHASE-III
DIAGNOSIS
MANAGEMENT
SKELETAL-REALTED EVENTS
SOLID CANCER
THERAPY
POSITRON-EMISSION-TOMOGRAPHY
CHEMOTHERAPY
RADIOTHERAPY
DOUBLE-BLIND
DISEASE
EXPRESSION
METASTASIS
ZOLEDRONIC ACID
PROSTATE-CANCER
SURVIVAL
BREAST-CANCER
BONE METASTASIS
CANCER
LUNG-CANCER
Keywords plus
2000
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018
2019
2020
2021
2022
Year
Value
1.00
0.75
0.50
0.25
0.00


B
Keywords plus distribution over time
BISPHOSPHONATES
ADENOCANCER
BONE COMPLICATIONS
SCINTIGRAPHY
PROGNOSTIC-FACTORS
MULTIPLE-MYELOMA
GEFITINIB
GROWTH
QUALITY-OF-LIFE
BONE
PHASE-III
DIAGNOSIS
MANAGEMENT
SKELETAL-REALTED EVENTS
SOLID CANCER
THERAPY
POSITRON-EMISSION-TOMOGRAPHY
CHEMOTHERAPY
RADIOTHERAPY
DOUBLE-BLIND
DISEASE
EXPRESSION
METASTASIS
ZOLEDRONIC ACID
PROSTATE-CANCER
SURVIVAL
BREAST-CANCER
BONE METASTASIS
CANCER
LUNG-CANCER
Keywords plus
2000
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014
2015
2016
2017
2018
2019
2020
2021
2022
Year
Value
1.00
0.75
0.50
0.25
0.00



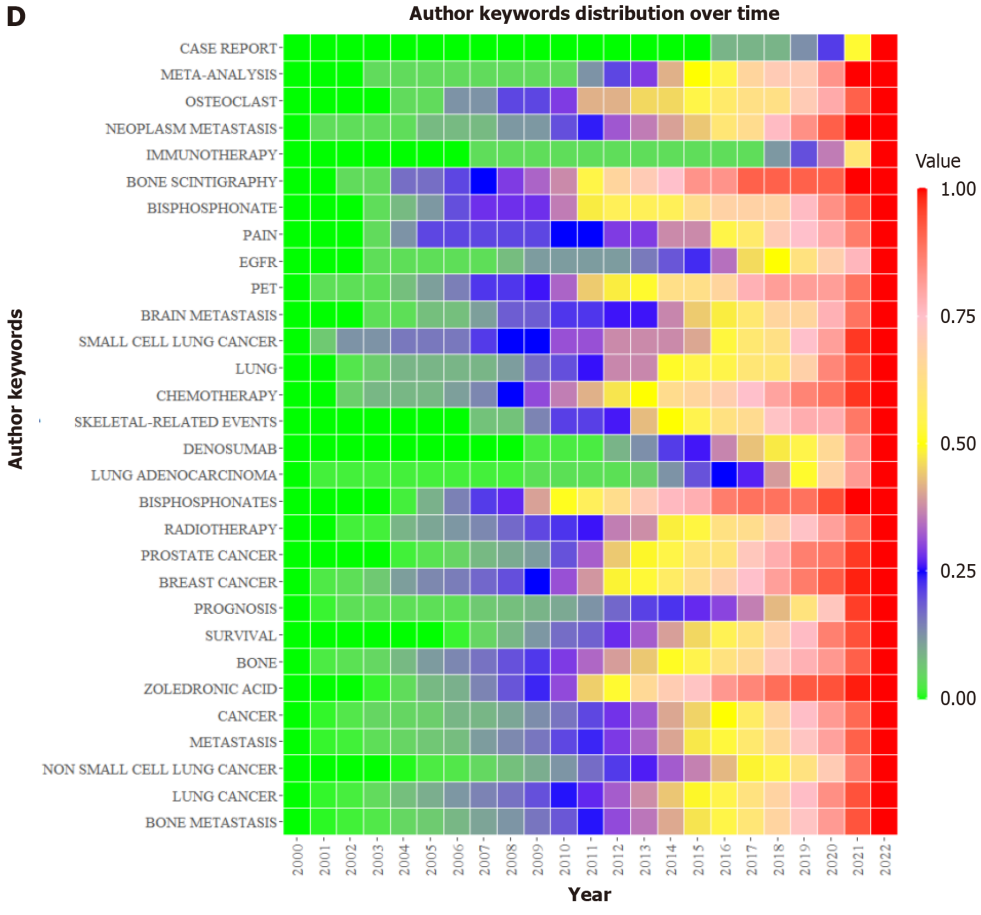


Figure 5 Keyword time heat map. A and B: Keywords plus; C and D: Authors' keywords. The A and C values represent the ratio of the frequency of a keyword

in each year to its highest frequency in a year. The B and D values represent the ratio of the total frequency of the keyword from 2000 to a certain year to its total frequency.

Main research directions in LCBM research

The volume of knowledge in LCBM research has been enriched gradually, mainly in the following areas. In terms of mechanism exploration, researchers have started to explore and identify key LCBM molecules through technological advancements, such as high-throughput sequencing. For example, Miki *et al*[30] and Liu *et al*[31] found that high expression levels of zinc finger E-box binding homology box 1 in LC cells leads to increased expression levels of parathyroid hormone-related protein, which prompts LC cells to undergo a continuous process of retention in the capillary bed, angiogenesis and proliferation, and causes the emergence of the site of metastasis, then metastasis to bone and an increase the number of BMs in the body. BM incidence is also increasing. In addition, primary tumours secrete several different factors and extracellular vesicles (EVs) into the circulation to reach bone, altering the bone microenvironment through mechanisms such as the action of calmodulin 11 in EVs with osteoblasts, eventually forming a pre-metastatic ecological niche in bone and preparing the tumour for BM[32,33]. When LC cells reach bone, since LC cells cannot directly damage the bone and colonize it, they must disrupt the RANKL/RANK/OPG pathway that forms a dynamic balance between osteogenesis and bone resorption, which is regulated by osteoblasts and osteoclasts. In this case, the action of the osteoclasts prevails and triggers the corresponding bone destruction and resorption, allowing LC cells to colonize and further invade and grow[34,35]. In addition, the mechanism of LCBM is similar to that of breast cancer BM[1]; thus, it is not surprising that the term "breast cancer" appears in our findings (Figure 6).

In terms of clinical treatments, the clinical exploration of targeted therapies and immunotherapies is in full swing. Numerous clinical studies have shown that both targeted therapy and immunotherapy can significantly extend survival and improve the prognosis of LCBM patients[36,37]. Among these, nivolumabtherapy may be effective in preventing bone destruction and relieving bone pain and other symptoms with long-term efficacy[38]. This is important for improving the quality of life for LCBM patients. Nevertheless, targeted therapies and immunotherapies for LCBM still face challenges, such as still being in the animal testing stage or drug resistance, and there is still a long way to go before they can be used as effective LCBM treatments[38-40].

Although palliative treatments have not been shown to make a significant positive impact on the survival of patients with BM, they can be highly effective for improving patient quality of life by providing rapid symptom relief[41,42]. Therefore, considering the unsatisfactory results of emerging therapies and the current absence of viable cures, palliative care is considered the best option for patients with BM to maintain a relatively high quality of life at the end of life[43].

Moreover, although adjuvant treatments, such as denosumab and zoledronic acid, can induce serious side effects, including hypocalcaemia, femoral fractures and osteonecrosis of the jaw, a large body of data suggests that they can play a significant role in prolonging the overall survival of LCBM patients and reducing the occurrence of a range of skeletal complications[14,15,44]. Therefore, it is not surprising that these treatments are major hot topics in LCBM research.

For clinical diagnosis, the commonly used PET/CT is useful for providing an accurate assessment of the risk LC patients have for developing BM and has great potential for therapeutic guidance[45,46]. This suggests that PET/CT may continue as a hot topic in the future. In addition, the scattering of certain mechanisms in the distribution of the abovementioned topics and the extensive connections with many application-related topics may reflect the fact that the relevant basic results are already driving the development of clinical applications.

Preliminary exploration of the molecular mechanisms of LCBM

The updated global molecular map of LCBM that we constructed suggests that the factors affecting the development of BM in LC patients may be closely related to abnormalities in the ribosomal pathway. This is largely consistent with existing reports. It has been reported that RPLP2, which encodes the eukaryotic 60S large ribosomal subunit P2, is significantly upregulated in patients with LCBM and is an important marker of a poor prognosis in these patients[47]. RPLP2 is also associated with DNA repair, cell division, apoptosis and the progression of multiple types of tumorigenesis [47]. Not coincidentally, Ebright *et al*[48] found that mice with breast cancer and high RPL15 expression levels have a greater likelihood of breast cancer cell metastasis to multiple organs. In LCBM tissue, the upregulation of COL6A1, which is closely related to the ribosome-related pathways, can enhance the proliferation and invasion of tumour cells and their adhesion to osteoblasts[49]. The upregulation of SMYD2, a transcriptional regulator, can activate the transcription of ribosomal small subunit protein 7 by binding to its promoter, thereby promoting the proliferation, migration, invasion and distant metastasis of LC cells[50]. Small nucleolar RNA can enhance downstream SCD1 translation and regulate lipid peroxidation and mechanistic target of rapamycin by promoting the 2′-O-methylation modification of the C3680 site on 28S rRNA to inhibit autophagy of LC cells and thereby promote LC cell growth and metastasis[51]. Ribosomal S6 kinase 2 can jointly promote CaMKIV signal transduction and enhance CREB activity through interaction with GDH1, thereby promoting LC cell metastasis[52]. More importantly, there are also *in vivo* experiments showing that the use of biomineralized metal-organic framework nanoparticles with protein toxins and nuclear factor-κB ligand receptor activator antibodies can reduce the occurrence of BM through the irreversible inactivation of ribosomes, a decrease in the number of LC cells and an interference with the interaction between LC cells and bone cells[53]. These indicate that ribosomes are very likely to be an important link in the occurrence of BM by LC cells and the interaction between LC cells and bone cells to cause skeletal-related events. This also reveals the clinical potential of this dual-protein therapy in the treatment of LC and LCBM. Furthermore, Bowley *et al*[54] found that high expression levels of RPL and RPS lead to aberrant ribosome synthesis that can promote the onset and progression of melanoma brain metastasis. A 20-year empirical report indicated

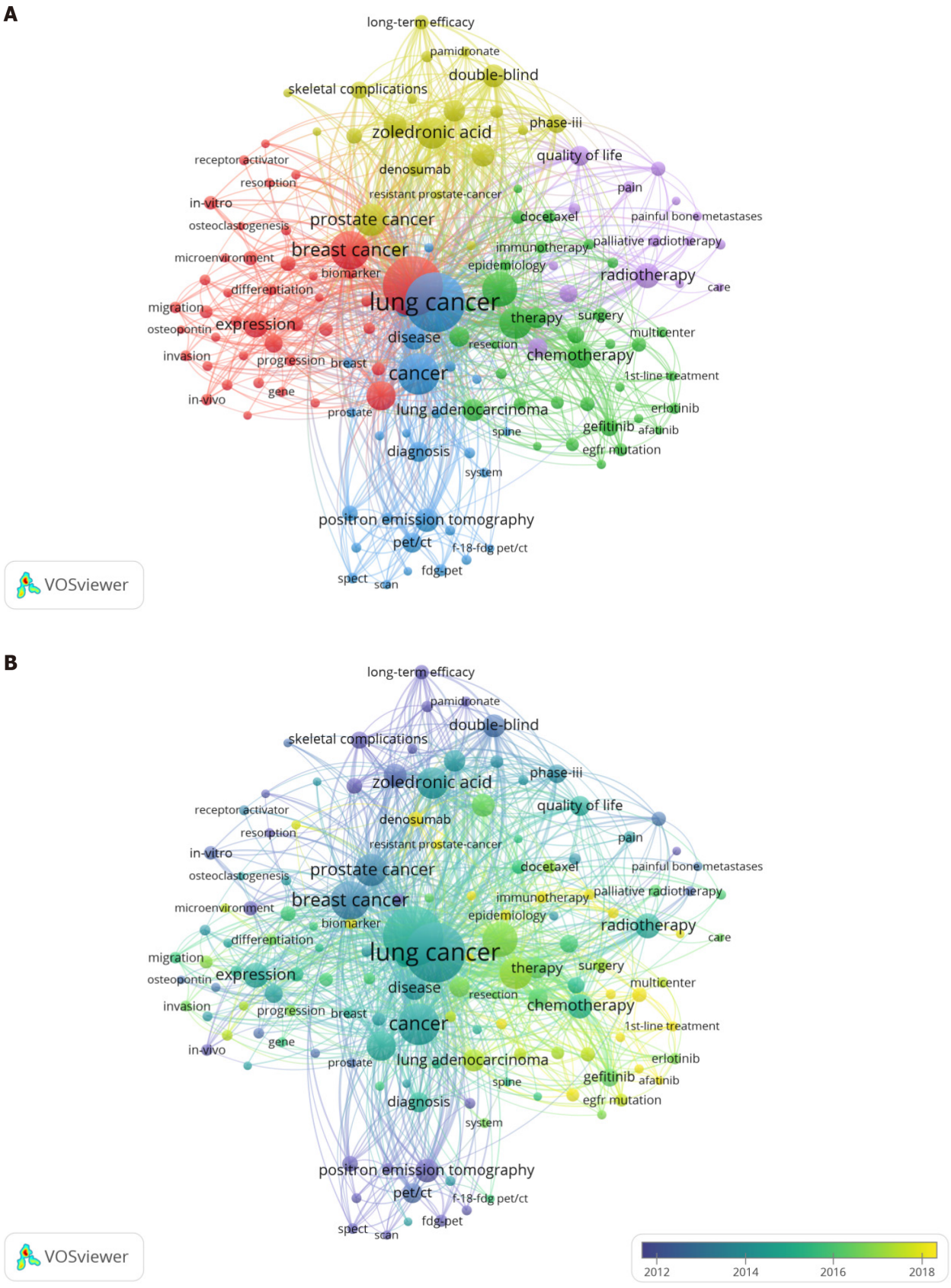


Figure 6 Analysis of the co-occurrence of all keywords. A: Network visualization map; B: Overlay visualization map. The small circle represents the keyword. The area of the small circle represents the frequency of the keyword. The colors of the different areas represent their categories. The lines of the connecting circles represent keywords that appear in an article at the same time.

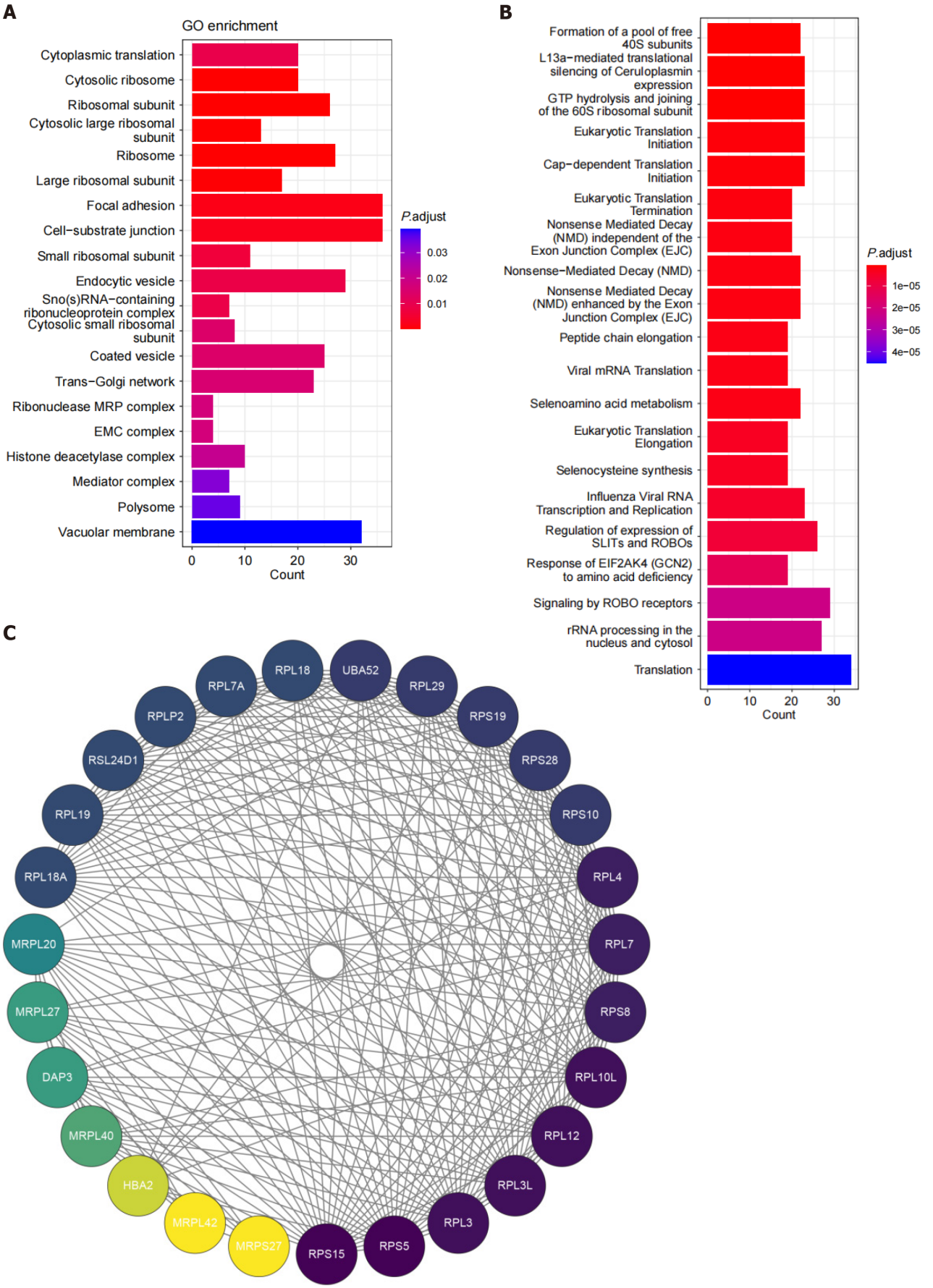


Figure 7 Molecular map of lung cancer bone metastasis. A: Bubble map of differentially expressed genes (DEGs) based on the Gene Ontology enrichment analysis; B: Bubble map of DEGs based on the Reactome enrichment analysis; C: Protein-protein interaction network diagram related to the ribosome pathway. GO: Gene Ontology.

that Diamond-Blackfan anaemia patients, which is caused by RPL or RPS mutations, has a high susceptibility to malignancy[55]. This is similar to the interaction between the RPS and RPL families in the results of the PPI analysis of the ribosome-related pathways. However, no direct evidence has confirmed that the ribosomal pathway in LC cells can also trigger BM through a similar action. In addition, focal adhesion-related pathways may also be closely associated with the BM of LC cells. One study that used microarray fractionation identified long-stranded noncoding RNAs that may mediate the development of spinal metastasisby affecting processes such as focal and cell adhesions in lung adenocarcinoma cells[56]. Another study claimed that the focal adhesion kinase/AKT/Rho-associated kinase pathway induces LC cell invasion and metastasis by interacting with bone bridge proteins, thus effectively inhibiting some protein activity [57]. These findings are similar to those of our enrichment analysis and fully suggest that focal adhesion may play a BM-promoting role in LC.

In addition, these pathways also play a role in other tumours or metastases. For example, the interaction between focal adhesion and extracellular matrix receptors can lead to changes in the actin cytoskeletal pathway and thereby promote the migration of LC cells to the brain[58]. MiR-215-5p downregulates the metastatic ability of colorectal cancer cells by regulating molecular biological processes, such as extracellular matrix-receptor interactions and focal adhesion[59]. The study revealed that miR-215-5p is likely to become a potential target for the treatment of the distant metastases of colorectal cancer. FSTL1 interacts with VIM to activate the focal adhesion signalling pathway and cytoskeleton rearrangement to achieve colorectal cancer liver metastasis[60]. EIF4A2, which is required for the binding of mRNA to ribosomes, plays an important role in the lung metastasis of colorectal cancer cells in vivo[61]. The significant molecular biological characteristics of LC brain metastasis include the significant enhancement of pathways related to ribosome activity and metabolic reprogramming[62]. In addition, there are studies claiming that ribosome biogenesis is a target with a strong clinical potential for treating many tumour metastases and alleviating drug resistance[63]. This also further illustrates the rationality of ribosome and focal adhesion-related pathways playing a role in LCBM. However, whether similar mechanisms are achieved in LCBM and what specific biological processes involve these mechanisms in the expression of molecules, transcriptional regulation, epigenetic modification and their clinical potential are still unknown. In the future, we plan to conduct more research that further explores and improves the data on the related biological mechanisms.

However, not all of the abovementioned molecular biological mechanisms appeared directly in the results of the bibliometric analysis of this study. This may be due to the fact that much of the literature was included in this study for the bibliometric analysis but only one dataset was used in constructing the LCBM-related molecular map. However, we believe that the direction of the basic research on LCBM is still weak. For example, the few existing studies mentioned earlier have shown that ribosomal and focal adhesion-related pathways may be the link that promotes BM by LC cells. This link is promising as a new target for the treatment of LCBM. However, as of now, no mature studies have explained the detailed processes of these pathways and developed clinical therapeutic diagnostics based on them. This is also illustrated by the fact that a dataset met our filtering requirements in multiple worldwide datasets. In addition, we investigated GTP hydrolysis and the joining of the 60S ribosomal subunit, translation, viral mRNA translation and NMD-related pathways in LCBM. However, no study has directly confirmed this. This requires further experimental validation. Thus, while clinical studies and new drugs have helped improve the survival prognosis for LC, there remains an urgent need for larger population data to enrich the molecular landscape of LCBM and more representative animal models to explain the biological behaviour of LCBM. This will lay the foundation for further advancements in the development of more effective diagnostic and therapeutic options for LCBM.

Limitations of the study and future research arrangements

This study has the following shortcomings: (1) It included only articles written in English that were of high quality and whose data could be comprehensively examined from the WOSCC. In the future, we should also include an analysis of articles on LCBM from other databases for supplementation and validation; (2) The study addressed only the current mainstream evolution of LCBM, hot directions, the current status of research on LCBM and future directions using limited analysis. We will further examine the valuable information behind these bibliometric indicators in the future; and (3) Although this study used various methods to analyse only the data sets that met the inclusion requirements for investigating the possible biological behaviour of LCBM and obtained strong suggestive and pioneering information, it lacks the verification of *in vivo* and *in vitro* experiments. In the future, we should conduct *in vivo* and *ex vivo* experiments to confirm the molecular biological mechanisms in LCBM.

CONCLUSION

In summary, LCBM has received extensive attention in recent years owing to targeted therapies and immunotherapies on the clinical research side and drug resistance mechanisms on the basic research side. Although the current regimens can provide improvements in patient quality of life, they cannot change the outcomes in patients with LCBM. This is mainly related to the poor effects of novel therapies and weak basic research. Future scientific research on LCBM can increase efforts on targeted therapies, immunotherapies and basic research to provide new concepts for the study of LCBM mechanisms and improve its prognosis.

ACKNOWLEDGEMENTS

Thanks to all the software and "Guangxi Key Laboratory of Medical Pathology" for providing technical support in computational pathology.

FOOTNOTES

Author contributions: He RQ, Huang ZG, Lu HP, Huang H, Yang DP, Tang ZQ, Yang X, Zhang HJ, Kong JL, and Chen G contributed to designing topics, guiding literature information extraction, guiding statistical analysis, and revising papers; Chen Y, Chen XS and Qv N contributed to literature downloads, information collection, statistical analysis, chart making, and draft paper writing; and all authors commented on previous versions of the manuscript. Chen Y and Chen XS contributed equally to this study, and share joint first authorship. Both Kong JL and Chen G give detailed guidance to this paper, which is of great significance. Therefore, they are both co-corresponding authors. All authors read and approved the final manuscript.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

PRISMA 2009 Checklist statement: The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.

Country of origin: China

ORCID number: Jin-Liang Kong 0000-0003-4065-7886; Gang Chen 0000-0002-4864-1451.

S-Editor: Wang JJ
L-Editor: A
P-Editor: Zhao YQ

REFERENCES

1 **Ben-Ghedalia-Peled N**, Vago R. Wnt Signaling in the Development of Bone Metastasis. *Cells* 2022; **11** [PMID: 36497192 DOI: 10.3390/cells11233934]
2 **Gouveia AG**, Chan DCW, Hoskin PJ, Marta GN, Trippa F, Maranzano E, Chow E, Silva MF. Advances in radiotherapy in bone metastases in the context of new target therapies and ablative alternatives: A critical review. *Radiother Oncol* 2021; **163**: 55-67 [PMID: 34333087 DOI: 10.1016/j.radonc.2021.07.022]
3 **Knapp BJ**, Devarakonda S, Govindan R. Bone metastases in non-small cell lung cancer: a narrative review. *J Thorac Dis* 2022; **14**: 1696-1712 [PMID: 35693589 DOI: 10.21037/jtd-21-1502]
4 **Zhou J**, Yang W, Liu Q. Cancer challenges worldwide and in China: preparing for the inevitable. *Sci China Life Sci* 2022; **65**: 442-444 [PMID: 34826096 DOI: 10.1007/s11427-021-2009-0]
5 **Cavers D**, Nelson M, Rostron J, Robb KA, Brown LR, Campbell C, Akram AR, Dickie G, Mackean M, van Beek EJR, Sullivan F, Steele RJ, Neilson AR, Weller D. Understanding patient barriers and facilitators to uptake of lung screening using low dose computed tomography: a mixed methods scoping review of the current literature. *Respir Res* 2022; **23**: 374 [PMID: 36564817 DOI: 10.1186/s12931-022-02255-8]
6 **Li W**, Guo Z, Zou Z, Alswadeh M, Wang H, Liu X, Li X. Development and validation of a prognostic nomogram for bone metastasis from lung cancer: A large population-based study. *Front Oncol* 2022; **12**: 1005668 [PMID: 36249042 DOI: 10.3389/fonc.2022.1005668]
7 **Zhou Y**, Zhu XP, Shi JJ, Yuan GZ, Yao ZA, Chu YG, Shi S, Jia QL, Chen T, Hu YH. Coronary Heart Disease and Depression or Anxiety: A Bibliometric Analysis. *Front Psychol* 2021; **12**: 669000 [PMID: 34149564 DOI: 10.3389/fpsyg.2021.669000]
8 **Wu H**, Cheng K, Guo Q, Yang W, Tong L, Wang Y, Sun Z. Mapping Knowledge Structure and Themes Trends of Osteoporosis in Rheumatoid Arthritis: A Bibliometric Analysis. *Front Med (Lausanne)* 2021; **8**: 787228 [PMID: 34888333 DOI: 10.3389/fmed.2021.787228]
9 **Kokol P**, Blažun Vošner H, Završnik J. Application of bibliometrics in medicine: a historical bibliometrics analysis. *Health Info Libr J* 2021; **38**: 125-138 [PMID: 31995273 DOI: 10.1111/hir.12295]
10 **Shen Y**, Lv Y. Dual targeted zeolitic imidazolate framework nanoparticles for treating metastatic breast cancer and inhibiting bone destruction. *Colloids Surf B Biointerfaces* 2022; **219**: 112826 [PMID: 36115265 DOI: 10.1016/j.colsurfb.2022.112826]
11 **Zulfiqar B**, Farooq A, Kanwal S, Asghar K. Immunotherapy and targeted therapy for lung cancer: Current status and future perspectives. *Front Pharmacol* 2022; **13**: 1035171 [PMID: 36518665 DOI: 10.3389/fphar.2022.1035171]
12 **Sung H**, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin* 2021; **71**: 209-249 [PMID: 33538338 DOI: 10.3322/caac.21660]
13 **Huang JF**, Shen J, Li X, Rengan R, Silvestris N, Wang M, Derosa L, Zheng X, Belli A, Zhang XL, Li YM, Wu A. Incidence of patients with bone metastases at diagnosis of solid tumors in adults: a large population-based study. *Ann Transl Med* 2020; **8**: 482 [PMID: 32395526 DOI: 10.21037/atm.2020.03.55]
14 **Bozzo A**, Deng J, Abbas U, Bhasin R, Deodat M, Wariach S, Sanger S, Axelrod D, Masrouha K, Turcotte R, Wilson D, Ghert M. Which Bone-

Modifying Agent is Associated with Better Outcomes in Patients with Skeletal Metastases from Lung Cancer? A Systematic Review and Network Meta-analysis. *Clin Orthop Relat Res* 2021; **479**: 2047-2057 [PMID: 33835092 DOI: 10.1097/CORR.0000000000001749]

15 **Cheng X**, Wei J, Ge Q, Xing D, Zhou X, Qian Y, Jiang G. The optimized drug delivery systems of treating cancer bone metastatic osteolysis with nanomaterials. *Drug Deliv* 2021; **28**: 37-53 [PMID: 33336610 DOI: 10.1080/10717544.2020.1856225]

16 **Nieder C**. Second re-irradiation: A delicate balance between safety and efficacy. *Phys Med* 2019; **58**: 155-158 [PMID: 30635148 DOI: 10.1016/j.ejmp.2019.01.004]

17 **Wu S**, Pan Y, Mao Y, Chen Y, He Y. Current progress and mechanisms of bone metastasis in lung cancer: a narrative review. *Transl Lung Cancer Res* 2021; **10**: 439-451 [PMID: 33569325 DOI: 10.21037/tlcr-20-835]

18 **Feng A**, Li Y, Li G, Wang Y, Wen Q, Yang Z, Tian K, Lv H, Guo L, Zhang S, Liu X, Jiang D. Genomic Features of Organ-Specific Metastases in Lung Adenocarcinoma. *Front Oncol* 2022; **12**: 908759 [PMID: 35912232 DOI: 10.3389/fonc.2022.908759]

19 **Li C**, Wang S, Xing Z, Lin A, Liang K, Song J, Hu Q, Yao J, Chen Z, Park PK, Hawke DH, Zhou J, Zhou Y, Zhang S, Liang H, Hung MC, Gallick GE, Han L, Lin C, Yang L. A ROR1-HER3-lncRNA signalling axis modulates the Hippo-YAP pathway to regulate bone metastasis. *Nat Cell Biol* 2017; **19**: 106-119 [PMID: 28114269 DOI: 10.1038/ncb3464]

20 **Lim SM**, Syn NL, Cho BC, Soo RA. Acquired resistance to EGFR targeted therapy in non-small cell lung cancer: Mechanisms and therapeutic strategies. *Cancer Treat Rev* 2018; **65**: 1-10 [PMID: 29477930 DOI: 10.1016/j.ctrv.2018.02.006]

21 **Liu C**, Wang M, Xu C, Li B, Chen J, Wang Z. Immune Checkpoint Inhibitor Therapy for Bone Metastases: Specific Microenvironment and Current Situation. *J Immunol Res* 2021; **2021**: 8970173 [PMID: 34877360 DOI: 10.1155/2021/8970173]

22 **Bhadresha K**, Upadhyay V, Brahmbhatt J, Mughal MJ, Jain N, Rawal R. In vitro model of predicting metastatic ability using tumor derived extracellular vesicles; beyond seed soil hypothesis. *Sci Rep* 2022; **12**: 20258 [PMID: 36424413 DOI: 10.1038/s41598-022-24443-8]

23 **Sharma R**, Sagoo NS, Haider AS, Sharma N, Haider M, Sharma IK, Igbinigie M, Aya KL, Aoun SG, Vira S. Iodine-125 radioactive seed brachytherapy as a treatment for spine and bone metastases: A systematic review and meta-analysis. *Surg Oncol* 2021; **38**: 101618 [PMID: 34153905 DOI: 10.1016/j.suronc.2021.101618]

24 **Chen J**, Zhou L, Liu X, Wen X, Li H, Li W. Meta-analysis of clinical trials to assess denosumab over zoledronic acid in bone metastasis. *Int J Clin Pharm* 2021; **43**: 2-10 [PMID: 32964403 DOI: 10.1007/s11096-020-01105-1]

25 **Huang Y**, Zhu L, Guo T, Chen W, Zhang Z, Li W, Pan X. Metastatic sites as predictors in advanced NSCLC treated with PD-1 inhibitors: a systematic review and meta-analysis. *Hum Vaccin Immunother* 2021; **17**: 1278-1287 [PMID: 33079622 DOI: 10.1080/21645515.2020.1823779]

26 **Guo X**, Ma W, Wu H, Xu Y, Wang D, Zhang S, Liu Z, Chekhonin VP, Peltzer K, Zhang J, Wang X, Zhang C. Synchronous bone metastasis in lung cancer: retrospective study of a single center of 15,716 patients from Tianjin, China. *BMC Cancer* 2021; **21**: 613 [PMID: 34039303 DOI: 10.1186/s12885-021-08379-2]

27 **Wang X**, Huang M, Xie W, Ding Q, Wang T. Eupafolin regulates non-small-cell lung cancer cell proliferation,migration, and invasion by suppressing MMP9 and RhoA *via* FAK/PI3K/AKT signaling pathway. *J Biosci* 2023; **48** [PMID: 36695419 DOI: 10.1007/s12038-022-00323-1]

28 **Han L**, Huang Z, Liu Y, Ye L, Li D, Yao Z, Wang C, Zhang Y, Yang H, Tan Z, Tang J, Yang Z. MicroRNA-106a regulates autophagy-related cell death and EMT by targeting TP53INP1 in lung cancer with bone metastasis. *Cell Death Dis* 2021; **12**: 1037 [PMID: 34718338 DOI: 10.1038/s41419-021-04324-0]

29 **Shen L**, Chen L, Wang Y, Jiang X, Xia H, Zhuang Z. Long noncoding RNA MALAT1 promotes brain metastasis by inducing epithelial-mesenchymal transition in lung cancer. *J Neurooncol* 2015; **121**: 101-108 [PMID: 25217850 DOI: 10.1007/s11060-014-1613-0]

30 **Miki T**, Yano S, Hanibuchi M, Kanematsu T, Muguruma H, Sone S. Parathyroid hormone-related protein (PTHrP) is responsible for production of bone metastasis, but not visceral metastasis, by human small cell lung cancer SBC-5 cells in natural killer cell-depleted SCID mice. *Int J Cancer* 2004; **108**: 511-515 [PMID: 14696114 DOI: 10.1002/ijc.11586]

31 **Liu Y**, Zhang N, Wang Y, Xu M, Liu N, Pang X, Cao J, Ma N, Pang H, Liu L, Zhang H. Zinc finger E-box binding homeobox 1 promotes invasion and bone metastasis of small cell lung cancer in vitro and in vivo. *Cancer Sci* 2012; **103**: 1420-1428 [PMID: 22632166 DOI: 10.1111/j.1349-7006.2012.02347.x]

32 **Xia C**, Dong X, Li H, Cao M, Sun D, He S, Yang F, Yan X, Zhang S, Li N, Chen W. Cancer statistics in China and United States, 2022: profiles, trends, and determinants. *Chin Med J (Engl)* 2022; **135**: 584-590 [PMID: 35143424 DOI: 10.1097/CM9.0000000000002108]

33 **He G**, Nie JJ, Liu X, Ding Z, Luo P, Liu Y, Zhang BW, Wang R, Hai Y, Chen DF. Zinc oxide nanoparticles inhibit osteosarcoma metastasis by downregulating β-catenin *via* HIF-1α/BNIP3/LC3B-mediated mitophagy pathway. *Bioact Mater* 2023; **19**: 690-702 [PMID: 35600978 DOI: 10.1016/j.bioactmat.2022.05.006]

34 **Feng Q**, Wang D, Feng J, Guo P, Geng C. Denosumab inhibits MCF-7 cell line-induced spontaneous osteoclastogenesis *via* the RANKL/MALAT1/miR-124 axis. *Transl Cancer Res* 2020; **9**: 2482-2491 [PMID: 35117607 DOI: 10.21037/tcr.2020.03.17]

35 **Chen F**, Han Y, Kang Y. Bone marrow niches in the regulation of bone metastasis. *Br J Cancer* 2021; **124**: 1912-1920 [PMID: 33758331 DOI: 10.1038/s41416-021-01329-6]

36 **Gen S**, Tanaka I, Morise M, Koyama J, Kodama Y, Matsui A, Miyazawa A, Hase T, Hibino Y, Yokoyama T, Kimura T, Yoshida N, Sato M, Hashimoto N. Clinical efficacy of osimertinib in EGFR-mutant non-small cell lung cancer with distant metastasis. *BMC Cancer* 2022; **22**: 654 [PMID: 35698083 DOI: 10.1186/s12885-022-09741-8]

37 **Meng C**, Ge X, Tian J, Wei J, Zhao L. Prognostic role of targeted therapy in patients with multiple-site metastases from non-small- cell lung cancer. *Future Oncol* 2020; **16**: 1957-1967 [PMID: 32687388 DOI: 10.2217/fon-2020-0289]

38 **Wang K**, Gu Y, Liao Y, Bang S, Donnelly CR, Chen O, Tao X, Mirando AJ, Hilton MJ, Ji RR. PD-1 blockade inhibits osteoclast formation and murine bone cancer pain. *J Clin Invest* 2020; **130**: 3603-3620 [PMID: 32484460 DOI: 10.1172/JCI133334]

39 **Hosoya K**, Fujimoto D, Morimoto T, Kumagai T, Tamiya A, Taniguchi Y, Yokoyama T, Ishida T, Matsumoto H, Hirano K, Kominami R, Tomii K, Suzuki H, Hirashima T, Tanaka S, Uchida J, Morita M, Kanazu M, Mori M, Nagata K, Fukuda I, Tamiya M. Clinical factors associated with shorter durable response, and patterns of acquired resistance to first-line pembrolizumab monotherapy in PD-L1-positive non-small-cell lung cancer patients: a retrospective multicenter study. *BMC Cancer* 2021; **21**: 346 [PMID: 33794809 DOI: 10.1186/s12885-021-08048-4]

40 **Tamiya M**, Fujikawa K, Suzuki H, Yokoyama T, Uenami T, Tamiya A, Sato Y, Saito G, Uchida J, Morita M, Hirashima T, Fukuda Y, Kanazu M, Hosoya K, Suzuki T, Ueno K, Fujimoto D, Kumagai T, Teramukai S. Classification and regression tree for estimating predictive markers to detect T790M mutations after acquired resistance to first line EGFR-TKI: HOPE-002. *Invest New Drugs* 2022; **40**: 361-369 [PMID: 35088212 DOI: 10.1007/s10637-021-01203-5]

41 **Leto G**. Current status and future directions in the treatment of bone metastases from breast cancer. *Clin Exp Pharmacol Physiol* 2019; **46**: 968-971 [PMID: 31330061 DOI: 10.1111/1440-1681.13139]

42 **Napoli A**, De Maio A, Alfieri G, Gasperini C, Scipione R, Campanacci L, Siepe G, De Felice F, Siniscalchi B, Chiurchioni L, Tombolini V, Donati DM, Morganti AG, Ghanouni P, Catalano C, Bazzocchi A. Focused Ultrasound and External Beam Radiation Therapy for Painful Bone Metastases: A Phase II Clinical Trial. *Radiology* 2023; **307**: e211857 [PMID: 36594834 DOI: 10.1148/radiol.211857]

43 **Ning MS**, Das P, Rosenthal DI, Dabaja BS, Liao Z, Chang JY, Gomez DR, Klopp AH, Gunn GB, Allen PK, Nitsch PL, Natter RB, Briere TM, Herman JM, Wells R, Koong AC, McAleer MF. Early and Midtreatment Mortality in Palliative Radiotherapy: Emphasizing Patient Selection in High-Quality End-of-Life Care. *J Natl Compr Canc Netw* 2021; **19**: 805-813 [PMID: 33878727 DOI: 10.6004/jnccn.2020.7664]

44 **Cheung E**, Borno HT. The limitations of today's clinical guidance: Atypical femoral fracture and long-term bone-modifying agents in the oncology setting. *J Oncol Pharm Pract* 2020; **26**: 1180-1189 [PMID: 32122232 DOI: 10.1177/1078155220907965]

45 **Lim CH**, Ahn TR, Moon SH, Cho YS, Choi JY, Kim BT, Lee KH. PET/CT features discriminate risk of metastasis among single-bone FDG lesions detected in newly diagnosed non-small-cell lung cancer patients. *Eur Radiol* 2019; **29**: 1903-1911 [PMID: 30315418 DOI: 10.1007/s00330-018-5764-9]

46 **Mankoff DA**, Katz SI. PET imaging for assessing tumor response to therapy. *J Surg Oncol* 2018; **118**: 362-373 [PMID: 29938396 DOI: 10.1002/jso.25114]

47 **Yang M**, Sun Y, Sun J, Wang Z, Zhou Y, Yao G, Gu Y, Zhang H, Zhao H. Differentially expressed and survival-related proteins of lung adenocarcinoma with bone metastasis. *Cancer Med* 2018; **7**: 1081-1092 [PMID: 29522283 DOI: 10.1002/cam4.1363]

48 **Ebright RY**, Lee S, Wittner BS, Niederhoffer KL, Nicholson BT, Bardia A, Truesdell S, Wiley DF, Wesley B, Li S, Mai A, Aceto N, Vincent-Jordan N, Szabolcs A, Chirn B, Kreuzer J, Comaills V, Kalinich M, Haas W, Ting DT, Toner M, Vasudevan S, Haber DA, Maheswaran S, Micalizzi DS. Deregulation of ribosomal protein expression and translation promotes breast cancer metastasis. *Science* 2020; **367**: 1468-1473 [PMID: 32029688 DOI: 10.1126/science.aay0939]

49 **Li N**, Liu M, Cao X, Li W, Li Y, Zhao Z. Identification of differentially expressed genes using microarray analysis and COL6A1 induction of bone metastasis in non-small cell lung cancer. *Oncol Lett* 2021; **22**: 693 [PMID: 34457048 DOI: 10.3892/ol.2021.12954]

50 **Wu L**, Kou F, Ji Z, Li B, Zhang B, Guo Y, Yang L. SMYD2 promotes tumorigenesis and metastasis of lung adenocarcinoma through RPS7. *Cell Death Dis* 2021; **12**: 439 [PMID: 33935284 DOI: 10.1038/s41419-021-03720-w]

51 **Wang K**, Wang S, Zhang Y, Xie L, Song X. SNORD88C guided 2'-O-methylation of 28S rRNA regulates SCD1 translation to inhibit autophagy and promote growth and metastasis in non-small cell lung cancer. *Cell Death Differ* 2023; **30**: 341-355 [PMID: 36376383 DOI: 10.1038/s41418-022-01087-9]

52 **Kang J**, Chun J, Hwang JS, Pan C, Li J, Boese AC, Young I, Malin CM, Kang Y, Gibbons DL, Sica G, Fu H, Ramalingam SS, Jin L, Kang S. EGFR-phosphorylated GDH1 harmonizes with RSK2 to drive CREB activation and tumor metastasis in EGFR-activated lung cancer. *Cell Rep* 2022; **41**: 111827 [PMID: 36516759 DOI: 10.1016/j.celrep.2022.111827]

53 **Niu Y**, Yang H, Yu Z, Gao C, Ji S, Yan J, Han L, Huo Q, Xu M, Liu Y. Intervention with the Bone-Associated Tumor Vicious Cycle through Dual-Protein Therapeutics for Treatment of Skeletal-Related Events and Bone Metastases. *ACS Nano* 2022; **16**: 2209-2223 [PMID: 35077154 DOI: 10.1021/acsnano.1c08269]

54 **Bowley TY**, Lagutina IV, Francis C, Sivakumar S, Selwyn RG, Taylor E, Guo Y, Fahy BN, Tawfik B, Marchetti D. The RPL/RPS gene signature of melanoma CTCs associates with brain metastasis. *Cancer Res Commun* 2022; **2**: 1436-1448 [PMID: 36407834 DOI: 10.1158/2767-9764.crc-22-0337]

55 **Quarello P**, Garelli E, Carando A, Cillario R, Brusco A, Giorgio E, Ferrante D, Corti P, Zecca M, Luciani M, Pierri F, Putti MC, Cantarini ME, Farruggia P, Barone A, Cesaro S, Russo G, Fagioli F, Dianzani I, Ramenghi U; AIEOP working group on Diamond Blackfan Anaemia. A 20-year long term experience of the Italian Diamond-Blackfan Anaemia Registry: RPS and RPL genes, different faces of the same disease? *Br J Haematol* 2020; **190**: 93-104 [PMID: 32080838 DOI: 10.1111/bjh.16508]

56 **Wang H**, Hu A, Liang Y, Wang K, Zhou X, Dong J. Genome-wide analysis of long non-coding RNA expression profile in lung adenocarcinoma compared to spinal metastasis. *Ann Transl Med* 2020; **8**: 1516 [PMID: 33313261 DOI: 10.21037/atm-20-7046]

57 **Kang CG**, Im E, Lee HJ, Lee EO. Plumbagin reduces osteopontin-induced invasion through inhibiting the Rho-associated kinase signaling pathway in A549 cells and suppresses osteopontin-induced lung metastasis in BalB/c mice. *Bioorg Med Chem Lett* 2017; **27**: 1914-1918 [PMID: 28359791 DOI: 10.1016/j.bmcl.2017.03.047]

58 **Gao Y**, Li G, Sun L, He Y, Li X, Sun Z, Wang J, Jiang Y, Shi J. ACTN4 and the pathways associated with cell motility and adhesion contribute to the process of lung cancer metastasis to the brain. *BMC Cancer* 2015; **15**: 277 [PMID: 25885339 DOI: 10.1186/s12885-015-1295-9]

59 **Machackova T**, Vychytilova-Faltejskova P, Souckova K, Trachtova K, Brchnelova D, Svoboda M, Kiss I, Prochazka V, Kala Z, Slaby O. MiR-215-5p Reduces Liver Metastasis in an Experimental Model of Colorectal Cancer through Regulation of ECM-Receptor Interactions and Focal Adhesion. *Cancers (Basel)* 2020; **12** [PMID: 33255928 DOI: 10.3390/cancers12123518]

60 **Gu C**, Wang X, Long T, Zhong Y, Ma Y, Hu Z, Li Z. FSTL1 interacts with VIM and promotes colorectal cancer metastasis *via* activating the focal adhesion signalling pathway. *Cell Death Dis* 2018; **9**: 654 [PMID: 29844309 DOI: 10.1038/s41419-018-0695-6]

61 **Chen ZH**, Qi JJ, Wu QN, Lu JH, Liu ZX, Wang Y, Hu PS, Li T, Lin JF, Wu XY, Miao L, Zeng ZL, Xie D, Ju HQ, Xu RH, Wang F. Eukaryotic initiation factor 4A2 promotes experimental metastasis and oxaliplatin resistance in colorectal cancer. *J Exp Clin Cancer Res* 2019; **38**: 196 [PMID: 31088567 DOI: 10.1186/s13046-019-1178-z]

62 **Woldmar N**, Schwendenwein A, Kuras M, Szeitz B, Boettiger K, Tisza A, László V, Reiniger L, Bagó AG, Szállási Z, Moldvay J, Szász AM, Malm J, Horvatovich P, Pizzatti L, Domont GB, Rényi-Vámos F, Hoetzenecker K, Hoda MA, Marko-Varga G, Schelch K, Megyesfalvi Z, Rezeli M, Döme B. Proteomic analysis of brain metastatic lung adenocarcinoma reveals intertumoral heterogeneity and specific alterations associated with the timing of brain metastases. *ESMO Open* 2023; **8**: 100741 [PMID: 36527824 DOI: 10.1016/j.esmoop.2022.100741]

63 **Elhamamsy AR**, Metge BJ, Alsheikh HA, Shevde LA, Samant RS. Ribosome Biogenesis: A Central Player in Cancer Metastasis and Therapeutic Resistance. *Cancer Res* 2022; **82**: 2344-2353 [PMID: 35303060 DOI: 10.1158/0008-5472.CAN-21-4087]

World Journal of Clinical Oncology

Submit a Manuscript: https://www.f6publishing.com

World J Clin Oncol 2024 June 24; 15(6): 783-785

DOI: 10.5306/wjco.v15.i6.783

ISSN 2218-4333 (online)

LETTER TO THE EDITOR

Predicting liver function after hemihepatectomy in patients with hepatocellular carcinoma using different modalities

Erfan Taherifard, Anwaar Saeed

Specialty type: Oncology

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's classification

Scientific Quality: Grade A
Novelty: Grade B
Creativity or Innovation: Grade B
Scientific Significance: Grade A

P-Reviewer: Dilek ON, Türkiye

Received: February 15, 2024
Revised: May 4, 2024
Accepted: May 20, 2024
Published online: June 24, 2024
Processing time: 129 Days and 19.3 Hours

Erfan Taherifard, Anwaar Saeed, Department of Medicine, University of Pittsburgh Medical Center, Pittsburgh, PA 15232, United States

Anwaar Saeed, UPMC Hillman Cancer Center, University of Pittsburgh Medical Center, Pittsburgh, PA 15232, United States

Corresponding author: Anwaar Saeed, MD, Associate Professor, Department of Medicine, University of Pittsburgh Medical Center, 5150 Centre Avenue, Pittsburgh, PA 15232, United States. saeeda3@upmc.edu

Abstract

In response to Dr. Yue *et al*'s study on prognostic factors for post-hemihepatectomy outcomes in hepatocellular carcinoma (HCC) patients, this critical review identifies methodological limitations and proposes enhancements for future research. While the study identifies liver stiffness measure and standard residual liver volume as potential predictors, concerns regarding small sample size, reliance on biochemical markers for safety assessment, and inadequate adjustment for confounding variables are raised. Recommendations for rigorous methodology, including robust statistical analysis, consideration of confounding factors, and selection of outcome measures with clinical components, are proposed to strengthen prognostic assessments. Furthermore, validation of novel evaluation models is crucial for enhancing clinical applicability and advancing understanding of postoperative outcomes in patients with HCC undergoing hemihepatectomy.

Key Words: Hepatocellular carcinoma; Liver cirrhosis; Hepatectomy; Liver failure; Standard residual liver volume; Liver stiffness

Core Tip: Methodological rigor is essential for evaluating post-hemihepatectomy outcomes in patients with hepatocellular carcinoma. This paper highlights limitations in the current research methodologies, emphasizing the need for robust statistical analysis and validation of novel evaluation models. Addressing these challenges will enhance prognostic assessments and advance our understanding of postoperative outcomes in this patient population.

Citation: Taherifard E, Saeed A. Predicting liver function after hemihepatectomy in patients with hepatocellular carcinoma using different modalities. *World J Clin Oncol* 2024; 15(6): 783-785
URL: https://www.wjgnet.com/2218-4333/full/v15/i6/783.htm
DOI: https://dx.doi.org/10.5306/wjco.v15.i6.783

TO THE EDITOR

We recently have read with great interest a recent article by Dr. Yue *et al*[1], "Clinical study of standard residual liver volume and transient elastography in predicting poor prognosis of patients after hemihepatectomy" which was published in *World Journal of Clinical Oncology*. The study aimed to investigate the risk factors associated with poor prognosis after hemihepatectomy in patients with hepatocellular carcinoma (HCC) secondary to hepatitis B cirrhosis. Their findings suggest that both preoperative and liver stiffness measure (LSM) and standard residual liver volume (SRLV) values could serve as independent risk factors for postoperative liver dysfunction, providing valuable insights into prognostic assessment for HCC patients undergoing hemihepatectomy. However, while acknowledging the significance of the findings in addressing the gap in the existing body of evidence on this topic, there are concerns regarding the study's validity that necessitate a cautious approach to interpreting the results.

One of the paramount considerations in this study, in addition to the small sample size that could potentially affect the statistical robustness of the findings, is the methodology employed and the outcome measure considered to assess the safety of hemihepatectomy in these patients. The reliance on biochemical assessments of liver function, such as abnormal international normalized ratio or total bilirubin levels, as indicators of operation safety, poses a significant limitation. The limitation of this approach lies in the possibility that patients may have exhibited these abnormal paraclinical liver profiles prior to the surgical intervention, thereby clouding the assessment of procedure safety when using this endpoint as the measure. The article did not provide information about the baseline status of the patients' liver function tests of the patients and also did not exclude patients with abnormal liver function from the study. Excluding patients with preexisting liver dysfunction could help ensure the integrity of the study's results by providing a clearer understanding of the impact of hemihepatectomy on liver function in individuals with HCC, where their liver function is not already compromised. Besides, the inclusion of outcome measures with clinical components in addition to liver dysfunction such as postoperative hepatic decompensation could offer a more comprehensive evaluation of the safety of hemihepatectomy in patients with HCC.

Second, while the authors employed a multivariable logistic regression model to evaluate the association between LSM value, SRLV, and postoperative liver dysfunction, they failed to address potential confounding factors or mitigate biases in their analysis model. It's recommended that relevant factors previously shown to be linked to the outcome variable, postoperative liver dysfunction, in the literature should be considered in the modeling analysis phase, where applicable [2-4]. This comprehensive approach would strengthen the study's validity and provide a more robust foundation for interpreting its findings.

Furthermore, the study introduced a new liver reserve evaluation model, integrating the Child-Pugh score with LSM values, which was reported in this study to have a superior accuracy in predicting postoperative liver function compared to the traditional Child-Pugh score. Based on the eligibility criteria of the study, however, patients with complications before the operation, such as hepatic encephalopathy, and abdominal dropsy, two items out of the five items of the Child-Pugh score and the six items of the new assessment model, were excluded. Therefore, the superiority of this new model may be subject to further scrutiny, and further studies with more diverse patient cohorts are needed to ascertain the performance of these two models.

In conclusion, while Dr. Yue *et al*'s study contributes valuable insights into prognostic evaluation for HCC patients undergoing hemihepatectomy, cautious interpretation is warranted due to methodological limitations and potential biases. Addressing these concerns through rigorous methodology and comprehensive analysis would enhance the reliability and applicability of the study's findings, thereby advancing our understanding of postoperative outcomes in this patient population.

FOOTNOTES

Author contributions: Taherifard E and Saeed A contributed to all stages of the work, including conceptualization, providing critical insights, and drafting of the manuscript. Both authors have read and approved the final manuscript.

Conflict-of-interest statement: The authors have no relevant financial or non-financial interests to disclose.

Country of origin: United States

ORCID number: Erfan Taherifard 0000-0002-9101-0321; Anwaar Saeed 0000-0001-8024-9401.

S-Editor: Qu XL
L-Editor: A
P-Editor: Zhao YQ

REFERENCES

1 **Yue ZQ**, Zhang P, Yan S, Ju LL, Wang HX, Yuan LX, Chen L, Wu JZ, Cao YL. Clinical study of standard residual liver volume and transient elastography in predicting poor prognosis of patients after hemihepatectomy. *World J Clin Oncol* 2023; **14**: 459-470 [PMID: 38059184 DOI: 10.5306/wjco.v14.i11.459]

2 **Ray S**, Mehta NN, Golhar A, Nundy S. Post hepatectomy liver failure - A comprehensive review of current concepts and controversies. *Ann Med Surg (Lond)* 2018; **34**: 4-10 [PMID: 30181871 DOI: 10.1016/j.amsu.2018.08.012]

3 **Xing Y**, Liu ZR, Yu W, Zhang HY, Song MM. Risk factors for post-hepatectomy liver failure in 80 patients. *World J Clin Cases* 2021; **9**: 1793-1802 [PMID: 33748228 DOI: 10.12998/wjcc.v9.i8.1793]

4 **Nishio T**, Taura K, Koyama Y, Ishii T, Hatano E. Current status of preoperative risk assessment for posthepatectomy liver failure in patients with hepatocellular carcinoma. *Ann Gastroenterol Surg* 2023; **7**: 871-886 [PMID: 37927928 DOI: 10.1002/ags3.12692]

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: office@baishideng.com
Help Desk: https://www.f6publishing.com/helpdesk
https://www.wjgnet.com