ISSN 2220-3249 (online)

World Journal of *Virology*

World J Virol 2021 November 25; 10(6): 288-331

Published by Baishideng Publishing Group Inc

World Journal of Virology

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INDEXING/ABSTRACTING

The *WJV* is now abstracted and indexed in PubMed, PubMed Central, China National Knowledge Infrastructure (CNKI), and Superstar Journals Database.

RESPONSIBLE EDITORS FOR THIS ISSUE

NAME OF JOURNAL
World Journal of Virology

ISSN
ISSN 2220-3249 (online)

LAUNCH DATE
February 12, 2012

FREQUENCY
Bimonthly

EDITORS-IN-CHIEF
Mahmoud El-Bendary, En-Qiang Chen

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https://www.wjgnet.com/2220-3249/editorialboard.htm

PUBLICATION DATE
November 25, 2021

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World J Virol 2021 November 25; 10(6): 288-300

DOI: 10.5501/wjv.v10.i6.288

ISSN 2220-3249 (online)

MINIREVIEWS

Protein-protein interactions: Methods, databases, and applications in virus-host study

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Author contributions: Farooq QUA and Li CH conceived of the review; Farooq QUA, Shaukat Z, and Aiman S reviewed the related literature; Farooq QUA drafted the original manuscript; Li CH read, revised, and approved the final manuscript; all the authors have read and approved the final manuscript.

Conflict-of-interest statement: The authors declare that they have no conflict of interest to disclose.

Supported by National Natural Science Foundation of China, No. 31971180 and No. 11474013.

Country/Territory of origin: China

Specialty type: Virology

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

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

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Abstract

Almost all the cellular processes in a living system are controlled by proteins: They regulate gene expression, catalyze chemical reactions, transport small molecules across membranes, and transmit signal across membranes. Even, a viral infection is often initiated through virus-host protein interactions. Protein-protein interactions (PPIs) are the physical contacts between two or more proteins and they represent complex biological functions. Nowadays, PPIs have been used to construct PPI networks to study complex pathways for revealing the functions of unknown proteins. Scientists have used PPIs to find the molecular basis of certain diseases and also some potential drug targets. In this review, we will discuss how PPI networks are essential to understand the molecular basis of virus-host relationships and several databases which are dedicated to virus-host interaction studies. Here, we present a short but comprehensive review on PPIs, including the experimental and computational methods of finding PPIs, the databases dedicated to virus-host PPIs, and the associated various applications in protein interaction networks of some lethal viruses with their hosts.

Key Words: Protein-protein interactions; Experimental and computational methods; Protein-protein interaction networks; Protein-protein interaction databases; Disease pathways; Protein-protein interaction applications

Core Tip: This paper provides a comprehensive review on protein-protein interactions (PPIs), including the experimental and computational methods of finding PPIs, the

Received: March 15, 2021
Peer-review started: March 15, 2021
First decision: April 6, 2021
Revised: April 19, 2021
Accepted: July 30, 2021
Article in press: July 30, 2021
Published online: November 25, 2021

P-Reviewer: Ahmad S
S-Editor: Gao CC
L-Editor: Wang TQ
P-Editor: Zhang YL

databases dedicated to virus-host PPIs, and the associated applications in the studies of some lethal viruses with their hosts. PPIs can be mapped into networks and innumerable novel insights into the functional organization of proteomes can be gained by analyzing the networks. Many studies have used network biology to construct PPI networks of lethal pathogens with their host *Homo sapiens* to dig deep down into the molecular constitution of the disease pathways, and have successfully found multiple potential drug targets against the viruses.

Citation: Farooq QUA, Shaukat Z, Aiman S, Li CH. Protein-protein interactions: Methods, databases, and applications in virus-host study. *World J Virol* 2021; 10(6): 288-300
URL: https://www.wjgnet.com/2220-3249/full/v10/i6/288.htm
DOI: https://dx.doi.org/10.5501/wjv.v10.i6.288

INTRODUCTION

Proteins have been declared as the chief representative of biological function[1]. It has been reported that more than 80% of proteins do not function alone[2], but instead often interact with each other or with other molecules like DNA or RNA to perform distinct cellular functions. Protein-protein interactions (PPIs) are thought to execute many biological processes including complex metabolic pathways and signaling cascades, and hence it is crucial to understand the particular nature of these associations[1,3].

De Las Rivas and Fontanillo[4] defined PPIs as "physical contacts with molecular docking between the proteins that occur in a cell or in a living organism *in vivo*". The physical contacts between the proteins should be specific and intentional, *i.e.*, evolved for a particular function. Protein interacting with other proteins can be in any form, *i.e.*, in binary, multi-protein complexes or in the form of long chains[1,4]. Proteins involved in a certain cellular pathway or biological process are often found to interact with each other repeatedly, suggesting that the proteins with associated functions are more likely to interact with each other[2,5]. Conversely, researchers can reveal the functions of unidentified or uncharacterized proteins if the proteins with which they are interacting are known[6,7]. The outcome of most of the cellular processes can be deciphered by protein interactions. The information about PPIs can help scientists find out potential drug targets by investigating the pathogen-host interaction network[8,9]. Therefore, it is significant to study PPIs for understanding the functions of proteins within a cell or a living organism.

EXPERIMENTAL METHODS TO DETECT PPIS

PPIs can be determined by different high-throughput experimental and computational methods which yield different types of PPI data. The high-throughput experimental techniques either identify the interactions directly or infer them indirectly based on different approaches[1,4]. In the following, the two main experimental methods, yeast two-hybrid (Y2H) and tandem affinity purification-mass spectrometry (MS), will be introduced.

Y2H

Y2H, also known as a binary method initially reported in 1989, is the most widely and commonly used interaction detection approach that identifies direct physical interactions between two proteins *in vivo*[10]. It detects the interactions between the query protein of interest and the protein library. In this approach, the former fused with the binding domain of a particular transcription factor is known as the bait and the latter fused with the activation domain of the transcription factor is referred to as the prey. If the bait and prey can interact with each other, they will bring together the two halves of the transcription factor to activate the transcription complex (shown in Figure 1), which transcribes the downstream reporter gene leading to the expression of the reporter gene[1,4,11]. The availability of many full genomes with the advancement of next-generation sequencing techniques allows us to use protein interactions to help

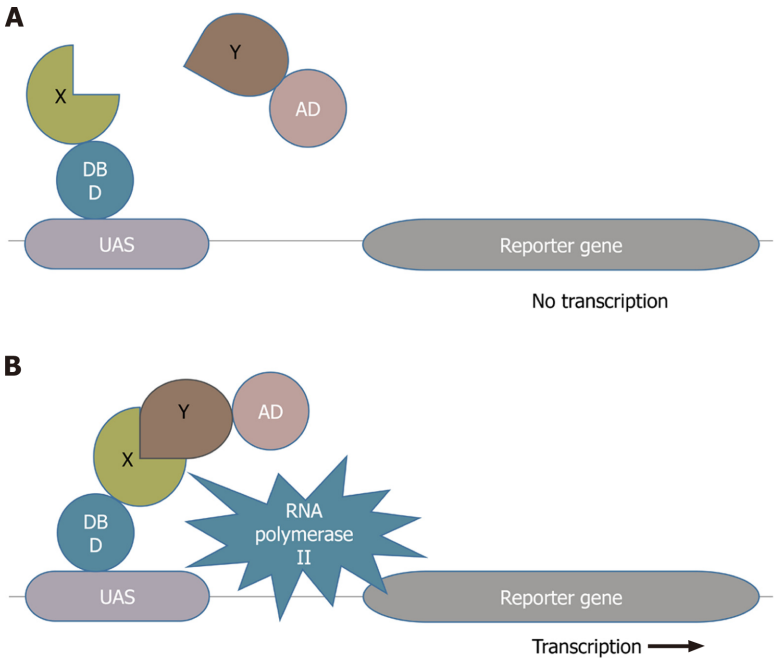

Figure 1 Yeast two-hybrid technique. A: There is no transcription of the reporter gene because the transcriptional factor is broken down into two halves; B: The reporter gene is being transcribed because the two halves of the transcription factor are brought together by the interaction between bait (X) and prey (Y) proteins[10]. DBD: DNA binding domain; AD: Activation domain; UAS: Upstream activation domain.

understand the functions of their gene products. Y2H has outranked the other experimental techniques and has become the system of choice for researchers in large-scale, high-throughput, and comprehensive investigations of PPIs. The complete proteomes of several pathogens including hepatitis C virus (HCV), bacteriophage T7, and vaccinia have been analyzed using the Y2H screen[12-14]. Several scientists have performed the comprehensive two-hybrid analysis of the yeast protein interactome, including the construction and analysis of PPI map of all possible associations between the yeast proteins[15-17].

Y2H has been used massively by scientists to infer physical interactions between macromolecules. It is advantageous because of its simple organization and easy detection for the transient interactions. However, despite its importance, there are certain disadvantages[10,18] which will be discussed in the section of experimental errors in PPI detection.

Tandem affinity purification-MS

MS is a powerful *in vitro* tool for the detection of macromolecular interactions. The principle of MS was explained extensively in one of our previous reviews[19]. MS allows us to identify polypeptide sequences by ionizing them and then detecting analyte ions based on their mass-to-charge ratios[20,21]. To interpret the mass spectra and detect PPIs, various MS-based methods have been developed so far. The MS-based detection of PPIs has become significant in the recent era especially for the large-scale investigations, through which high-throughput and high confidence PPIs can be identified[22,23]. These MS-based technologies include cross-linking MS (CLMS)[24], tandem affinity purification MS (TAP-MS)[25,26], and several others.

TAP-MS is a conventional MS-based qualitative method to study protein functions and interactions. Sinz[27] and Yugandhar *et al*[28] have extensively reviewed CLMS, which is a more recent and advanced MS technique for interpreting protein interaction networks. Many scientists have been working on the techniques using MS for finding potential interactors where true positives are segregated and prioritized from false positives. Gavin *et al*[29] and Collins *et al*[30] developed score-based methods to infer high-accuracy physical interactions.

According to the EMBL-EBI statistics (https://www.ebi.ac.uk/intact/about/statistics?conversationContext=2), TAP-MS has overtaken Y2H as a major source of generating PPI data.

Compared with Y2H which detects only binary interactions, TAP-MS is a co-complex method which determines both direct and indirect associations between proteins *in vitro*. In this technique, a TAP tag is fused at the C- or N-terminus of a

protein of interest (the bait), which has two independent binding regions, allowing two successive affinity purification steps. The most common TAP tag consists of two immunoglobulin G binding repeats of Protein A from *Staphylococcus aureus* (ProtA) and a calmodulin-binding peptide which are separated by a tobacco etch virus protease cleavage site. In TAP, a group of protein complexes can be caught by a tagged bait protein in a pull-down assay, which are called prey proteins[2,4,31]. The prey proteins interacting with the bait are separated *via* sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE) and then identified by MS[18,32].

In addition to the tandem affinity purification, there is another co-complex method called co-immunoprecipitation (CoIP) for determining PPIs. The interaction data derived from co-complex methods cannot be used to infer binary interactions directly, and the related algorithms are needed to interpret the pairwise interactions from the experimental data[4].

Experimental errors in PPI detection

High-throughput experimental approaches for determining PPIs are very efficient, but they also have some limitations. They have a high possibility of false negative and false positive errors. False positives in an experimental system are those interactions that do not occur in the system naturally. One reason for the false positives in Y2H can be the auto-activation of transcription by the bait protein itself or sometimes the transient interactions that are not always specific, *i.e.*, the interactors can be the sticky prey proteins fused with the bait protein and chosen by Y2H analysis[4,10,33]. The precise percentage of the false-positive interactions in Y2H is not well known but the estimated rate of the inaccurate interactions is about 50%, which is quite a big percentage, yet still Y2H is one of the most powerful interaction determining methods [2,10]. Additionally, the experimental system for determining PPIs faces false negative errors too, *i.e.*, some interactions cannot be identified due to the flaws in the experimental system. In Y2H, most of the interactions between membrane proteins are undetectable. Hence, it is important to choose the Y2H design thoughtfully based on the type of cellular proteome. Sometimes in Y2H, very weak transient interactions escape from being identified by the method[10].

Co-complex methods also encounter errors in their interaction detection mechanisms. There can be sticky prey proteins in the TAP pull down assay that are detected by the method as interacting partners of the bait protein. The TAP is an *in vitro* technique, which means that it is not sure whether the interactions that occur *in vitro* will surely exist *in vivo*. Additionally in TAP, the very transient interactions often vanish due to the series of purification levels[1,2]. Another drawback of co-complex methods is that they might analyze all the elements of a protein complex which certainly may not have direct interactions with each other[10] (crossed links in Figure 2).

PPI studies do not just rely on Y2H or affinity purification methods, and due to the false positives and false negatives, several other methods have also been made into practice by researchers for PPI detection. Some of these *in vitro* techniques are CoIP [18], protein microarrays[34], protein-fragment complementation[35], X-ray crystallography, and nuclear magnetic resonance spectroscopy[36].

COMPUTATIONAL METHODS FOR PREDICTING PPIS

As discussed in the previous section, experimental methods for PPI detection have many limitations including a high percentage of false positives, high cost, and being significantly laborious and time-consuming. Besides, due to the completion of various genome sequencing projects, it is necessary to speed up to find the functional linkages between proteins. Thus, the computational prediction of PPIs seems to be very crucial. Now, computational methods are being practiced successfully to evaluate and analyze the interaction data generated by high-throughput experimental approaches as well as to predict novel PPIs by gaining insights from the already known interactions.

The computational methods are a quick and low-cost alternative to the traditional experimental techniques to predict PPIs. An important advantage of computational methods over the experimental ones is that we can study proteins by mapping the pairwise associations into a comprehensive network according to their distinct functional level[1,37]. Table 1 lists some of the important *in silico* methods of PPI prediction.

Table 1 List of some important computational methods of protein-protein interaction prediction along with their brief descriptions

Method	Description	Ref.
In silico two-hybrid (I2H)	The I2H method is based on the detection of direct physical associations between the interacting proteins and it relies on the presumption that in order to maintain the protein function reliable, the interacting proteins should go through coevolution	Pazos and Valencia[38]
Ortholog-based approach	It is a sequence-based approach that uses a pairwise local search algorithm to obtain the similarities between the query protein pairs and the known interaction pairs. It is dependent upon the homologous nature of the target proteins	Lee *et al*[39]
Gene fusion	Also known as Rosetta stone method. According to this method, some of the proteins with single domains fuse together in one organism and form a multi-domain protein in another organism	Enright *et al*[40]
Domain-pairs-based approach	This method predicts the interactions between proteins by the domain-domain interactions	Wojcik and Schächter[41]
Gene expression	An indirect way to predict PPIs. Based on the concept that the proteins translated from the genes that belong to the common expression profiling clusters more likely interact with each other than the proteins translated from the genes that belong to different clusters	Grigoriev[42]
Structure-based approaches	It predicts protein-protein interactions based on the structural similarity	Zhang *et al*[43]
Phylogenetic tree	This method predicts protein-protein interactions based on the concept that the interacting proteins show similarity in their evolution history	Sato *et al*[44]

PPI: Protein-protein interaction.

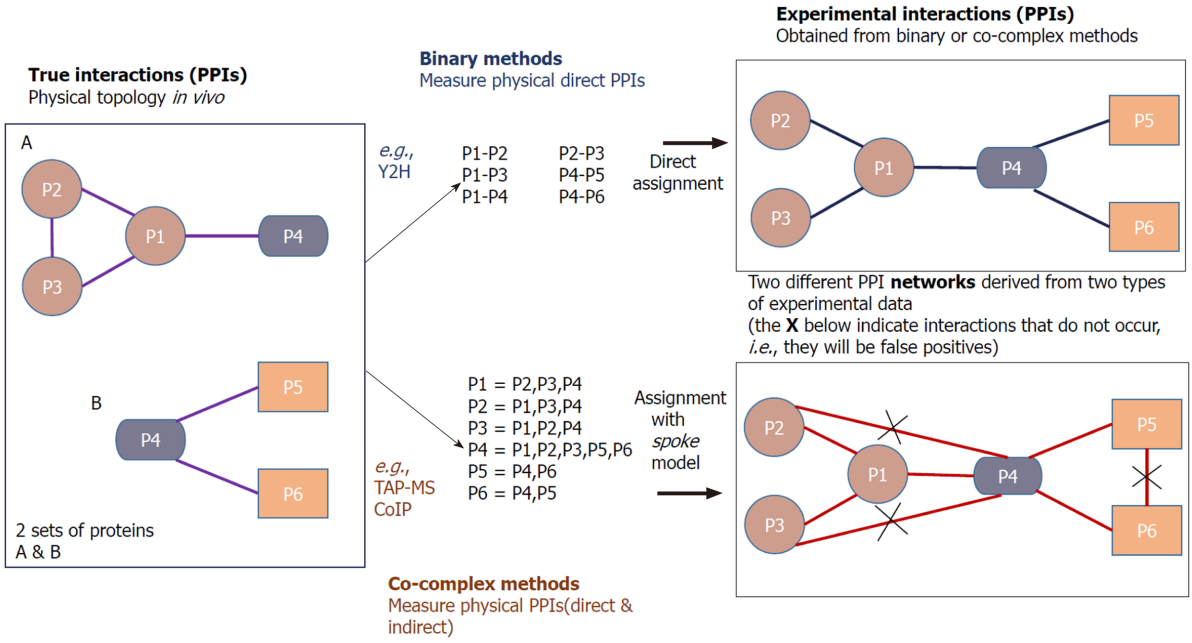

Figure 2 Binary and co-complex methods to determine protein-protein interactions. Yeast two-hybrid (Y2H) and tandem affinity purification mass spectrometry are the two most extensively used approaches for detecting protein-protein interactions. Given here are the two sets of proteins (4 proteins in set A while 3 proteins in set B) in the left panel and the connections show the genuine interactions between them. The right side shows the experimentally determined interaction network among the six proteins. The network in the upper right shows the interactions derived from Y2H, and the network in the lower right shows the interactions got from co-complex method, in which three of the interactions inferred do not exist[4]. PPI: Protein-protein interaction; TAP-MS: Tandem affinity purification mass spectrometry; CoIP: Co-immunoprecipitation.

PPI DATABASES

The continuous increase in PPI data produced by high-throughput technologies needs the formation of biological repositories where these data should be stored in an effective and organized way. The data in the publicly available PPI databases makes it much easier to analyze different types of interactions according to our concerns[37]. There are more than 100 repositories accessible online related to PPI data[45]. Here we will discuss the most popular databases (see Table 2) of PPI information that have

Table 2 List of popular protein-protein interaction databases with total numbers of interactions and last updated time

PPI database	URL	Total interactions	Last updated	Ref.
STRING	http://string-db.org/	> 2000 mio	2020	Szklarczyk *et al*[50]
BioGrid	http://thebiogrid.org/	1746922	2021	Oughtred *et al*[47]
HPIDB	https://hpidb.igbb.msstate.edu/index.html	69787	2019	Ammari *et al*[51]
MINT	https://mint.bio.uniroma2.it/	131695	2012	Zahiri *et al*[3] and Licata *et al*[55]
DIP	https://dip.doe-mbi.ucla.edu/dip/Main.cgi	81923	2017	Zahiri *et al*[3] and Salwinski *et al*[56]
IntAct	http://www.ebi.ac.uk/intact/	1130596	2020	Orchard *et al*[52]
HPRD	http://www.hprd.org/	41327	2010	Zahiri *et al*[3] and Keshava Prasad *et al*[57]

PPI: Protein-protein interaction; URL: Uniform resource locator.

been used by most of the researchers worldwide and contain experimentally verified virus-host PPIs.

Biological General Repository for Interaction Datasets

The Biological General Repository for Interaction Datasets (BioGRID) is a publicly retrievable and comprehensive database which stores experimentally determined PPI data of almost all important model organisms[3,46]. It has constantly being updated and according to the February 2021 release, it carries 1740000 non-redundant protein and genetic interactions collected from 70000+ publications[47]. The current version of BioGrid (v 4.3.194) themed curation projects focuses on curated interactions of different diseases including coronavirus disease 2019 (COVID-19), ubiquitin-proteosome system, fanconi anemia, glioblastoma, and autophagy.

Search Tool for Retrieval of Interacting Genes

Search Tool for Retrieval of Interacting Genes (STRING) is equipped with the complete information about the functional relationships between proteins. The current version STRING v11.0 contains interaction data of 5090 organisms that is the highest number of organisms covered by any PPI database. The major assets of STRING database are its exhaustive coverage, confidence scoring of the interactions, and its intuitive user interface[48,49]. Currently, the database covers 3123056667 PPIs which are the sum of high-confidence and low-confidence interactions. An important new feature in the current version of STRING is that users can perform Gene Ontology and KEGG analysis of their input which has provided ease in gene-set enrichment analysis[50].

HPIDB

HPIDB is a curated database that contains host-pathogen interaction data. Developed in 2010, it is updated yearly and presents new versions. Currently, it contains protein interaction data between 66 hosts and 668 infectious pathogen species. The number of unique interactions is 69787 according to the last update (July 29, 2019). The pathogenic species that can be found superabundantly in HPIDB are influenza virus, herpes virus, papillomaviruses, *Saccharomyces cerevisiae*, and several others[51].

IntAct

Developed in 2002, IntAct is a freely available molecular interaction data source and contains the data obtained from literature curation or deposited directly by the researchers. In 2013, IntAct and MINT joined their efforts and started the MINTACT project to maximize the coverage and curation output[52].

International Molecular Exchange Consortium databases

The International Molecular Exchange Consortium (IMEx) is an international consortium established by the joint efforts of prime public interaction databases including DIP, IntAct, HPIDB, MINT, BioGRID, MatrixDB, I2D, and some others. BIND and MPIDB which used to be large PPI databases are also members of IMEx but they no longer are active anymore. The data in IMEx is a comprehensive and integrated consortium of databases recording meta data for PPIs in a standard PSI-MS format and is available for all the researchers to re-use and re-analyze. Over the last two decades, there has been a massive increase in protein interaction data and out of

all the resources, IMEx is the only source which is providing up to the minute information regarding protein interactions and annotations[45,53,54].

Some protein interaction databases are dedicated to a specific viral pathogen for example HCVPro[58] containing the data on PPIs between HCV and human. VirHostNet[59] covers an extensive range of human specific viruses and contains nearly 22000 virus-human PPIs.

APPLICATIONS OF PPIS IN DISEASE NETWORKS AND IN VIRUS-HOST RELATIONSHIP

Bacteria and viruses are the major pathogens affecting humans on earth. Bacterial infections can be eradicated by using antibiotics, and viruses not easy to be eliminated can only be inhibited in their growth. Viruses depend entirely on their hosts and infect hosts often by virus-host protein interactions[54]. PPIs can be mapped into networks and innumerable novel insights into the functional organization of proteomes can be gained by analyzing the networks. Several protein interaction network construction and visualization tools are available, including Cytoscape[60], BioLayout[61], and VisANT[62]. Analyzed by these tools, PPI networks can provide the differences between normal and the diseased states, and thus the fundamental knowledge about the disease can be obtained based on the related pathways revealed through the analyses of PPI network, *i.e.*, by looking into the subnetworks constructed by the proteins involved in the disease[1,63]. Protein interaction networks can help find new disease-related genes by the presumption that the neighboring genes of the disease-causing gene are expected to be causing the same disease or involved in causing some similar diseases (Figure 3)[64]. Various researchers have been using network biology to study pathogen-host relationship at the molecular level, which ultimately helps in identifying key viral proteins and their human targets and helps scientists in further biological investigations.

The quickly developing knowledge of human interactome map and the availability of different host-pathogen networks have paved us the way for a better understanding of diseases. Viral genomes code for a very small number of proteins, which makes it easy to understand the mechanisms of the infections by viruses[64,65]. The network-based study on the infection of host with viral pathogenesis is progressing over time. In one of our previous studies, we constructed a comprehensive protein interaction network of HCV with its host *Homo sapiens*[66] and found out many crucial insights into finding potential targets against HCV and some other disease pathways, such as cancer pathways (Figure 4). In fact, certain viruses such as papilloma and herpesvirus have been reported to be causing up to 20% of the cancers[67]. Additionally, virus-host relationship was also studied by us for human papillomavirus[68], influenza A virus (IAV)[69], and dengue virus with *Homo sapiens*. Interestingly, in a study performed by Navratil *et al*[70], they compared a set of virus targets with a list of 1729 human genetic disease-related proteins, and found that 13% of human virus targets are also linked with at least one human genetic disease. In short, there are so many types of viruses causing a wide variety of infections worldwide. From Ebola virus outbreak in Africa to Middle East respiratory syndrome coronavirus outbreak, viruses have killed thousands of people with no specific effective treatment. Every viral infection involves PPIs between the virus and its host including the viral entry to the host cell and hijacking the host transcription machinery. Identification of PPIs between the viruses and their hosts lets us understand the infection mechanisms of the viruses and find a way to combat the infections using antiviral drugs or vaccines[71].

When we talk about human interactome, more than 645000 PPIs are reported to be disease-associated while only 2% of these proteins are targeted by drugs[72]. The reason for most of the proteins considered to be undruggable is because of the absence of detectable pockets for binding ligands[73]. Researchers have been significantly investigating PPI inhibitors and stabilizers and have succeeded in developing new technologies that have enabled the systematic discovery of drugs focused on PPIs[74, 75]. Zhang *et al*[76] and Robertson and Spring[77] have extensively explained the use of peptidomimetics to find the 'hot spots' on the protein surfaces for drug design. Targeting PPIs for designing therapeutics was once considered a difficult and impossible task. However, during the past two decades, the concept has changed and PPI drug targets have gained considerable interest from the scientific community. Some researchers have been conducting drug target studies in both wet and dry labs, hoping to find potential hot spot regions in PPIs' binding interfaces for designing therapeutic drugs. The discovery of small molecule PPI modulators by the emergence

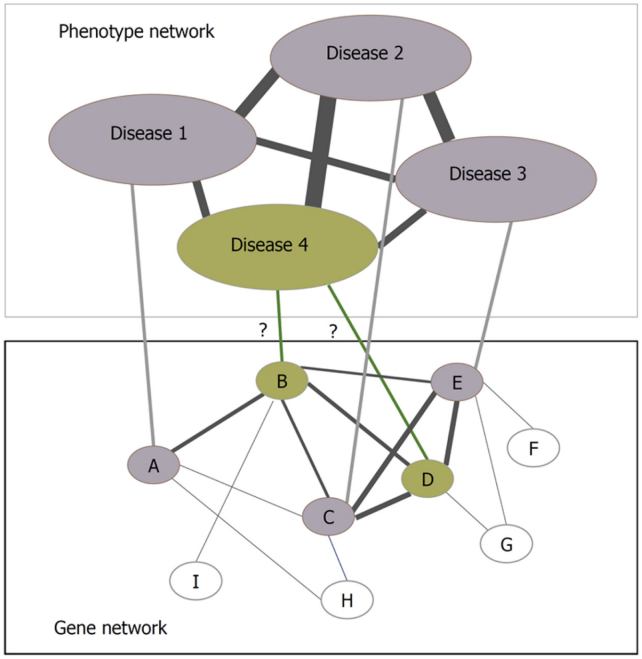

Figure 3 Protein interaction networks can help find new disease-related genes. The concept depicts that diseases 1, 2, and 3 are caused subsequently by genes A, C, and E, and the genes causing disease 4 are unknown but disease 4 is phenotypically associated with diseases 1, 2, and 3. If the known genes, *i.e.*, A, C, and E are closely associated functionally, it can be hypothesized that genes B and D are the cause of disease 4[86].

of new technologies has made the PPIs significant drug targets[72,78]. Until now, three databases have been dedicated to modulators of PPIs: (1) 2P2I database[79]; (2) TIMBAL[80]; and (3) iPPI-DB[81], and more than 40 PPIs have been targeted successfully[82]. To our knowledge, some of the druggable hotspots for well-studied PPI targets identified by various studies are: MDM2/p53, IL-2/IL-2Ra, HPV-11 E2/HPV-11 E1, TNF-α/TNFR1, and several others[83].

Currently, much focus has been diverted towards the recent COVID-19 pandemic, and many studies have been carried out to combat the deadly virus experimentally and computationally. Gordon *et al*[84] performed affinity purification-MS and identified 332 physical interactions between human proteins and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) proteins. The study helped researchers to dig deep down into the host molecular machineries and identify potential hotspots for developing therapeutic compounds to treat COVID-19. PPI identification will also help in predicting the behavior of the virus and the biological processes targeted by the virus. Khorsand *et al*[85] developed a three-layered network model to predict SARS-CoV-2-human PPIs and reported the most central human proteins in the network by investigating host proteins that are targeted by the viral proteins.

In summary, network biology has become the focus of attention in the recent era by scientists for understanding diseases and the biological processes targeted by the disease. Interaction networks are playing a significant role in understanding virus-host relationship and drug discovery.

CONCLUSION

The study on PPIs is not just a new field, but a new era in study of virus-host relationships, and we can say that PPIs are at the core of any viral infection. Scientists can use PPIs to gain innumerable novel insights into the functional constitution of a proteome by analyzing all kinds of network parameters. Network biology can help scientists find many potential drug targets that might be involved in certain viral pathways. Many studies have used network biology to construct protein interaction networks of lethal pathogens such as HCV, IAV, dengue virus, and human papilloma virus with their host *Homo sapiens* to dig deep down into the molecular constitution of the disease pathways, and have successfully found multiple potential drug targets against the viruses. In short, the future of PPI-induced network biology is quite clear and scientists can perform plenty of useful studies against any disease or pathway.

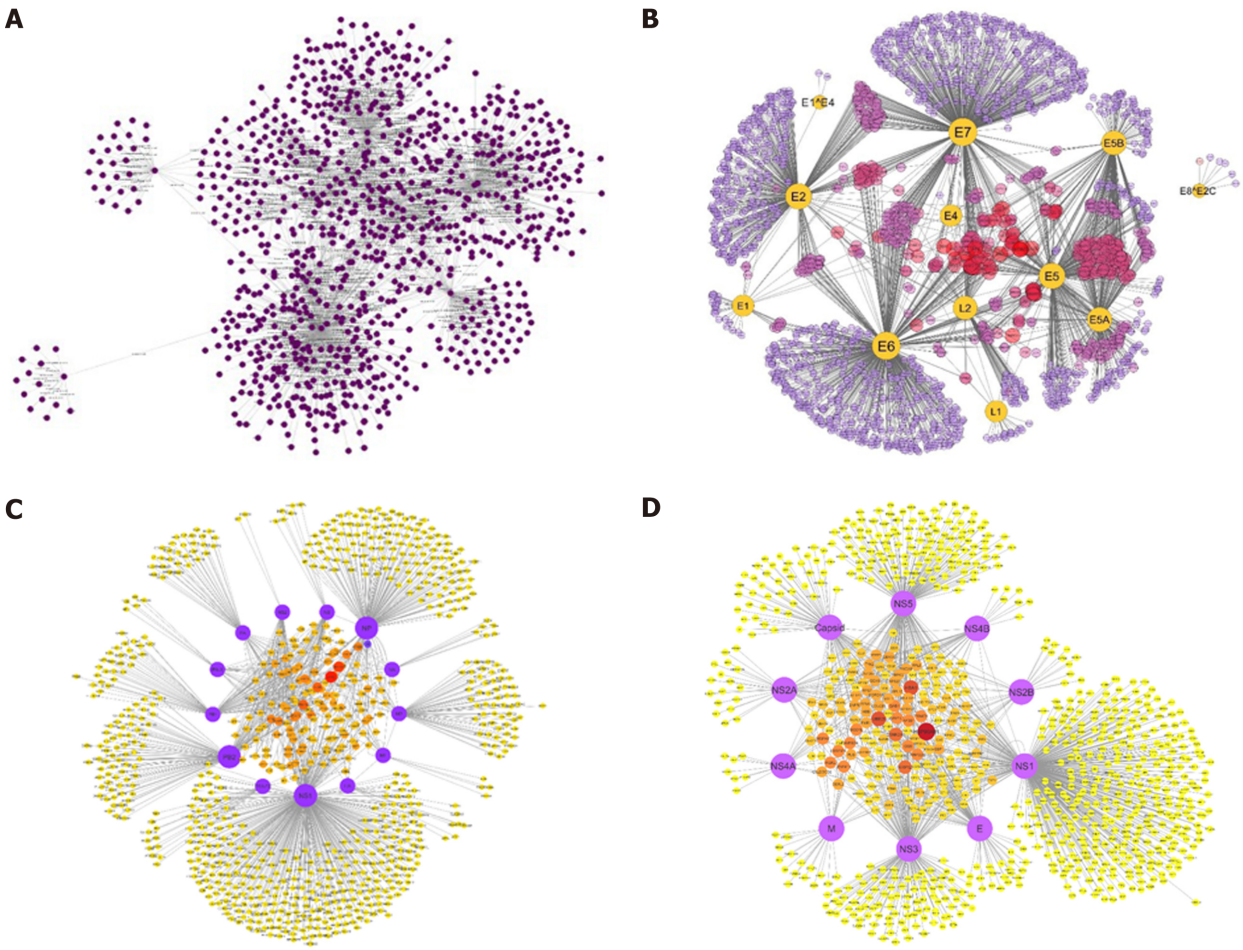

Figure 4 Comprehensive protein interaction networks of hepatitis C virus, human papillomavirus, influenza A virus, and dengue virus with host *Homo sapiens* constructed in Cytoscape by literature curated experimentally verified and computationally predicted protein-protein interactions. The network explains virus-host relationship between the infectious agents and host factors which contribute to disease pathways in human body. A: Hepatitis C virus; B: Human papillomavirus; C: Influenza A virus; D: Dengue virus.

Computational prediction of PPIs has become a mandatory tool for finding out the functionalities of unknown proteins.

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World Journal of Virology

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

World J Virol 2021 November 25; 10(6): 301-311

DOI: 10.5501/wjv.v10.i6.301

ISSN 2220-3249 (online)

MINIREVIEWS

Impact of COVID-19 on liver disease: From the experimental to the clinic perspective

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Conflict-of-interest statement: No conflicts of interest.

Country/Territory of origin: Spain

Specialty type: Gastroenterology and hepatology

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

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

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Abstract

Coronavirus disease 2019 (COVID-19) has caused a global pandemic unprecedented in over a century. Although severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a predominantly respiratory infection, various degrees of liver function abnormalities have been reported. Pre-existing liver disease in patients with SARS-CoV-2 infection has not been comprehensively evaluated in most studies, but it can critically compromise survival and trigger hepatic decompensation. The collapse of the healthcare services has negatively impacted the diagnosis, monitoring, and treatment of liver diseases in non-COVID-19 patients. In this review, we aim to discuss the impact of COVID-19 on liver disease from the experimental to the clinic perspective.

Key Words: SARS-CoV-2; COVID 19; Liver disease; Transaminases

Core Tip: The outbreak of coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has posed a critical threat to global public health. Beyond the respiratory symptoms, some patients with COVID-19 show liver damage. In this scenario, it has been suggested that there might be a specific relationship between SARS-CoV-2 infection and liver injury.

Received: March 24, 2021
Peer-review started: March 24, 2021
First decision: May 5, 2021
Revised: May 18, 2021
Accepted: August 13, 2021
Article in press: August 13, 2021
Published online: November 25, 2021

P-Reviewer: Fallatah H
S-Editor: Wang JL
L-Editor: Webster JR
P-Editor: Xing YX

Citation: Gato S, Lucena-Valera A, Muñoz-Hernández R, Sousa JM, Romero-Gómez M, Ampuero J. Impact of COVID-19 on liver disease: From the experimental to the clinic perspective. *World J Virol* 2021; 10(6): 301-311
URL: https://www.wjgnet.com/2220-3249/full/v10/i6/301.htm
DOI: https://dx.doi.org/10.5501/wjv.v10.i6.301

INTRODUCTION

Coronaviruses are enveloped single-stranded RNA viruses belonging to the Coronaviridae family and Orthocoronavirinae subfamily[1]. They cause zoonotic infections in humans, predominantly associated with the upper respiratory tract[2]. Two coronaviruses caused relatively recent epidemics: severe acute respiratory syndrome coronavirus (SARS-CoV) in 2003 and the Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012[3].

The outbreak of coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), first reported in China in December 2019, has posed a critical threat to global public health[4,5]. Therefore, COVID-19 has been declared an international public health emergency by the World Health Organization (WHO). As of 21st March 2021, more than 122 million confirmed cases and over 2.7 million deaths have been reported[6] (Figure 1).

In most cases, the infection is followed by a benign course with usual characteristics of viral pneumonia, such as fever, dry cough, and lymphopenia. A relatively low percentage of patients require hospitalization and intensive care for acute respiratory failure secondary to diffuse alveolar damage. There is also an important incidence of extrapulmonary manifestations, such as acute kidney injury, cardiovascular disease, neurological disorders, or hypercoagulation[7].

On the other hand, some patients with COVID-19 show different degrees of liver injury, showing mainly elevated serum transaminase and lactate dehydrogenase levels and hypoalbuminemia[8-10]. In this scenario, it has been suggested that there might be a specific relationship between SARS-CoV-2 infection and liver injury. Thus, this article reviews the impact of COVID-19 on liver disease from the experimental to the clinic perspective.

MECHANISMS OF LIVER DAMAGE IN COVID-19

Direct cytopathic effect of SARS-CoV-2

As with SARS-CoV, angiotensin-converting enzyme 2 (ACE2) appears to be the susceptible receptor for SARS-CoV-2 and is expressed in more than 80% of lung alveolar cells. *In vitro* studies from the SARS epidemic identified ACE2 as the host receptor for viral entry[11], but in this new coronavirus, a recent study showed a 10-20-fold higher receptor binding affinity[12].

The hepatic distribution of ACE2 is quirky; it is highly expressed in the endothelial layer of small blood vessels but not in the sinusoidal endothelium. Indeed, a study revealed that the ACE2 cell surface receptor was more highly expressed in cholangiocytes (59.7%) than hepatocytes (2.6%). Both the level of ACE2 expression in cholangiocytes and lung alveolar type 2 cells are similar, indicating that the liver could be a potential target for SARS-CoV-2[13].

SARS-CoV-2 exerts a cytopathic effect by directly binding to ACE2 positive cholangiocytes. They are involved in liver physiology functions, including regeneration and adaptive immune response mechanisms; thus, their disruption can cause hepatobiliary damage. This is supported by cholestatic markers, including gamma-glutamyl transferase, which can be found in some case reports of COVID-19[14-16]. Permissiveness to SARS-CoV-2 infection was observed in a human organoid model of liver ductal organoids. In this experiment, the viral infection damaged the barrier and bile acid transporting functions of cholangiocytes through the dysregulation of genes implicated in tight junction formation and bile acid transportation, supporting the susceptibility of cholangiocytes in SARS-CoV-2 infection[17]. On the other hand, a significant increase in mitotic cells and ballooned hepatocytes was observed in liver biopsies of patients with SARS-associated coronavirus infection, suggesting that it may induce apoptosis of liver cells[18]. Moreover, the virus was detected in liver tissue, although the viral load was relatively low.

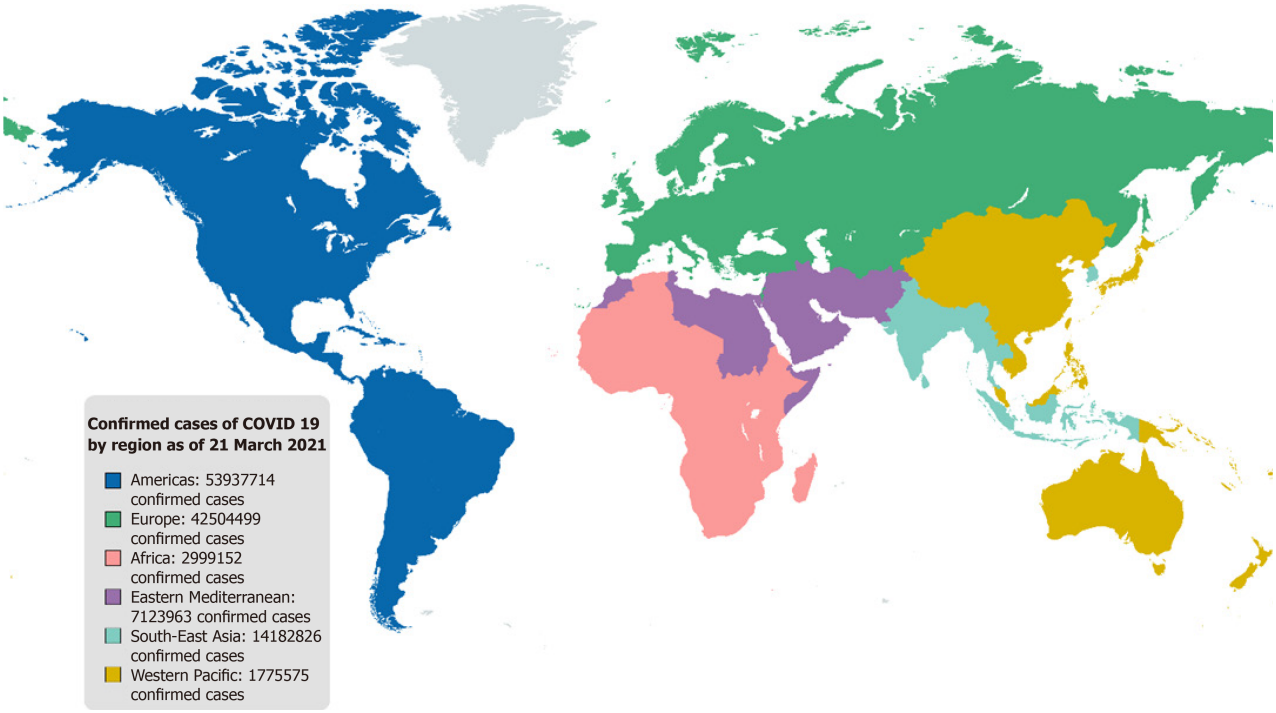

Figure 1 Coronavirus outbreak: World map of confirmed cases (updated March 21st, 2021). COVID-19: Coronavirus disease 2019.

A recent study demonstrated that SARS-CoV-specific protein 7a induces apoptosis *via* a caspase-dependent pathway in cell lines of different organs, including the liver, further confirming the supposition that SARS-CoV-2 directly affects the liver tissue [19]. Nevertheless, some authors have refuted this hypothesis since the disorder of liver function is usually mild, and there is no evidence that late-onset symptoms are associated with greater liver damage[20].

Host inflammatory response to SARS-CoV-2

As we have described previously, liver injury in patients with COVID-19 might be due to the viral infection in liver cells. However, it might also be due to other causes such as drug-induced liver injury and systemic inflammation induced by cytokine storm or pneumonia-associated hypoxia[15].

A well-established driver of liver injury is hepatic inflammation, involving the activation of innate immune cells and the release of cytokines[21] (Figure 2). A possible cause of liver injury in COVID-19 can be the dysregulation of the innate immune response. Noticeable activation of inflammatory markers, including abnormal levels of C-reactive protein (CRP), lymphocytes, neutrophils, and cytokines - particularly interleukin-6 (IL-6) - are found in patients with COVID-19[15,22-24]. In some of the available case series of COVID-19, a correlation between lymphopenia and liver injury was observed. Moreover, high levels of CRP and a low lymphocyte count were independent risk factors for liver injury. Notably, lymphopenia in COVID-19 studies was observed in 63% to 70.3% of patients, and those with lower lymphocyte counts were more susceptible to fatal outcomes[22]. These impairments have also been reported in some systemic viral infections, such as cytomegalovirus, herpes simplex virus, Epstein-Barr virus, parvovirus, and adenovirus, in which we can also observe the immune activation and inflammation caused by circulating cytokines[25]. Furthermore, some studies have reported higher serum pro-inflammatory cytokines and chemokine levels in patients with abnormal liver function than those with normal liver function[22]. Hence, these data point to a relationship between liver damage and the inflammatory response induced by SARS-CoV-2 infection.

Drug-induced liver injury

The liver is involved in the metabolism of many drugs, and some therapeutic agents used to treat SARS-CoV-2 show potential hepatotoxicity. For example, alanine transaminase (ALT) and aspartate aminotransferase (AST) elevations were reported in 4%-

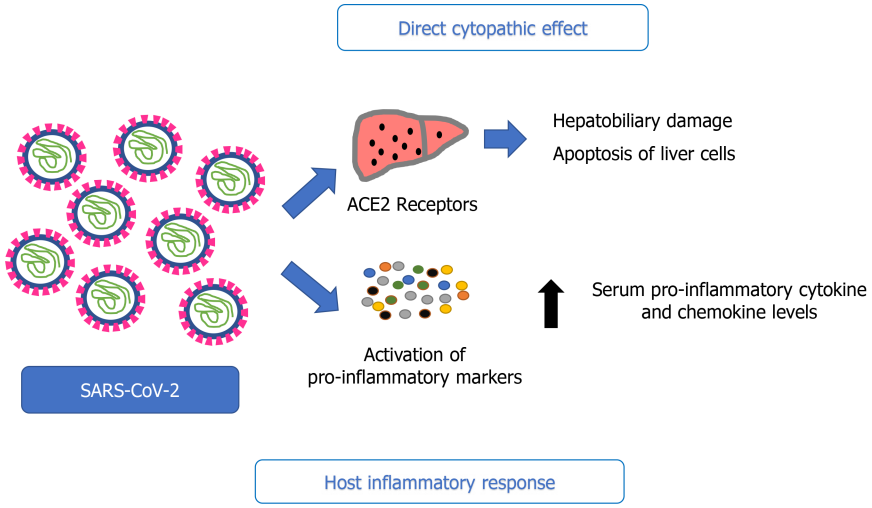

Figure 2 Proposed mechanisms of liver injury related to severe acute respiratory syndrome coronavirus 2 infection. SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2.

6% of patients treated with remdesivir[26], and tocilizumab can also cause mild elevations in liver transaminases[27]. However, it seems unlikely that the leading cause of liver injury is the treatment as alterations in liver transaminases are usually reported at the time of hospital admission.

FREQUENCY OF LIVER IMPAIRMENT IN COVID-19

The prevalence of elevated liver enzymes occurs between 15% and 53% of patients with COVID-19[28,29]. The difference in the prevalence may be related to the exclusion of patients with a previous liver disease[30]. The most common disorder includes elevated aminotransferases (AST and ALT) up to 1-2 times the upper limit of normal, while the elevation of total bilirubin (TB) and alkaline phosphatase is less common. A recent study of 2073 patients with SARS-CoV-2 infection documented liver abnormalities in 1282 (61.8%) of these patients. This study observed liver impairment more frequently in patients with severe COVID-19. Besides, they described cholestasis and mixed types of liver abnormalities as independent variables associated with death [31]. Another recent meta-analysis that included more than 5000 patients from 26 studies also demonstrated that liver function (AST, ALT, and TB) was related to intensive care unit (ICU) admission and non-fatal severe complications[32]. The findings of these studies make us consider incorporating the liver profile to the routine inflammatory markers at the time of hospital admission in patients with SARS-CoV-2 infection to improve their management and anticipate the prognosis.

ROLE OF PRE-EXISTING CHRONIC LIVER DISEASE

Several studies have analyzed the impact of chronic liver disease on SARS-CoV-2 infection. First, the prevalence of underlying liver disease in hospitalized patients for COVID-19 ranges between 0.6% to 1.4%[33]. A recent international registry of 745 patients with chronic liver disease (CLD) and SARS-CoV-2 has observed an increased risk of major adverse outcomes and death in cirrhotic patients according to the Child-Pugh class[34]. In this study, a significant increase in ICU requirement, renal replacement therapy and rates of death according to Child Pugh class [A (19%), B (35%), C (51%)] has been observed. These findings have been demonstrated by other studies, proving an increase in complications and mortality with cirrhosis and Child Pugh score of 9 or more[35]. The mortality rate was 32%-34% for cirrhotic patients compared with CLD without cirrhosis, who had a similar risk of mortality than patients without any liver disease[36,37]. Although lung disease remained the predominant cause of death, SARS-CoV-2 infection appeared to precipitate acute hepatic decompensation in patients with cirrhosis[35,38].

The preexisting liver disease most often associated with COVID-19 is metabolic-associated fatty liver disease (MAFLD)[39]. A multicenter retrospective study by Zheng *et al*[40] demonstrated that the severity of SARS-CoV-2 infection was greater in patients with MAFLD and obesity[40,41].

There is disparity in the data on chronic hepatitis infection prevalence in COVID-19, with percentages ranging from 0.1% to more than 10% in relation to the prevalence of hepatotropic viruses in the area[42,43]. In China, a country with an intermediate-to-high prevalence of chronic hepatitis B (HBV) infection, a surprisingly low prevalence of chronic HBV in COVID-19 patients has been observed. Anugwom *et al*[44] have reported an incidence of HBV of 1.36%, while the corresponding rates of HBV ranged from 7% to 11% in patients without SARS-CoV-2. This may be explained by "immune exhaustion", as HBV infection provides an inadequate immune response during SARS-CoV-2 infection. Furthermore, chronic hepatitis infection does not appear to lead to a worse prognosis in patients with COVID-19[45]. This fact could be explained by the potential *in vitro* antiviral effect of the drugs used for chronic infection with hepatotropic viruses (inhibitors of the NS5A protein or nucleotide analogs)[46-48]. However, this has not been demonstrated in patients under active *in vivo* treatment[49,50].

Finally, the role of SARS-CoV-2 on autoimmune liver diseases has not been adequately evaluated. However, some studies have not observed a higher incidence of SARS-CoV-2 infection and severe complications than in the general population[51,52]. To date, there is no evidence to support or recommend a decrease or change in the immunosuppressive therapy in these patients.

SARS-COV-2 INFECTION AND LIVER TRANSPLANT PATIENTS

In liver transplant (LT) recipients, immunosuppression following LT may increase the likelihood of SARS-CoV-2 infection[53,54]. Once a transplant recipient is infected with SARS-CoV-2, the virus may remain to infect for a longer duration due to higher viral titers and a prolonged replication period[55]. On the other hand, immunosuppressive agents could ameliorate the systemic inflammation induced by the cytokine storm[56].

Some of the available case series in LT patients with COVID-19 show a higher hospitalization rate (40%-86.5%)[54,57-60], as well as an increase in ICU admission requirements and invasive ventilation[59,61] in these patients. Despite the fact that mortality in LT recipients by COVID-19 is approximately 20% (8%-30.6%)[54,57-60], several studies have not shown that COVID-19-related mortality could be greater in hospitalized LT patients than in the general population[59,61]. Risk factors associated with poor prognosis in LT patients with COVID-19 are older age[53,57,60,62], diabetes mellitus[57-60], chronic kidney disease[60], and liver injury (ALT > 2 times ULN)[58].

On the other hand, it has not been clearly established how the immunosuppressive treatment influences the prognosis of LT patients with COVID-19. For instance, a study showed that mycophenolate might increase the risk of severe COVID-19 in a dose-dependent manner[54], while tacrolimus use has had a positive independent effect on survival[60]. Therefore, it could be concluded that increased disease severity and mortality in LT patients with COVID-19 is caused by the higher prevalence associated with comorbidities than by the effect of immunosuppressive treatment. In fact, in LT recipients without COVID-19, international guidelines recommend against reducing immunosuppression. However, in patients diagnosed with COVID-19, a reduction of immunosuppression should be considered.

IMPACT OF THE PANDEMIC IN THE HEPATOLOGY UNITS

Since the beginning of the SARS-CoV-2 pandemic, the healthcare system has supported a substantial impact, and the hepatology units have suffered notable changes in the organization. The access to medical consultations has been limited due to the hospital overload and strict orders to stay at home, the resources and staff reallocation have caused a decrease in the care of non-COVID pathologies. After a year of pandemic, the epidemiology of COVID-19 has proven to be unpredictable, however, it is urgent to anticipate and plan to mitigate the consequences of the pandemic and achieve a dynamic balance of resources.

Screening of hepatocellular carcinoma

The prevalence of hepatocellular carcinoma (HCC) has increased globally in the last

few years. Significant efforts have been made to decrease HCC-related mortality. For this reason, HCC screening using imaging tests at regular intervals has been implemented and standardized, and is strongly recommended by the international clinical guidelines[63,64].

A recent retrospective study comprising 127 hospitals showed a significant diminution of HCC control during the pandemic, showing screening rates below 50% compared to 2019[65]. Other studies have also found similar results with a decreased HCC surveillance by ultrasound and, more important than this, a decrease in diagnostic tests such as computed tomography or magnetic resonance imaging[66]. Thus, a significant increase in HCC-related mortality could be observed in the next months.

On the other hand, the COVID-19 pandemic has also impacted the management of HCC patients. A recent French multicenter study of 670 patients described a significant decrease in the rate of patients with HCC referred for specific treatment. The rate of patients with a treatment delay of more than one month was higher in 2020 compared to 2019 (21.5% *vs* 9.5%, $P < 0.001$)[67].

Screening of hepatitis C virus

There were 1.7 million incident cases and 400000 deaths attributable to hepatitis C virus (HCV) in 2015; thus, this viral hepatitis has been recognized as a major cause of death[68]. A breakthrough in HCV treatment occurred in 2013 with the introduction of direct-acting antivirals. For this reason, the WHO approved some ambitious aims to eliminate HCV by 2030, including the reduction of new HCV cases by 80% and HCV-related deaths by 65% for 2030.

The pandemic has caused a slowing or even the halt of HCV elimination programs. The impact of COVID-19 on viral hepatitis in a recent survey has shown that only 47 (36%) of 132 responders could access viral hepatitis testing, and 28 people on treatment for hepatitis were unable to access their medication at this time[69]. Although the real impact is far from being seen, different studies have been carried out to measure the future consequences. Blach *et al*[70] using a previously validated Markov model, compared a "no delay" *vs* "one-year delay" scenario in elimination programs and evaluated changes in HCV liver-related deaths and liver cancer. Over the next ten years, the authors estimated that a single-year delay scenario could result in over 72300 liver-related deaths and 44800 excess cases of HCC[71].

To avoid the delay in HCV elimination programs, integrated circuits for massive and combined HCV, HBV, and SARS-CoV-2 diagnosis have been proposed[72]. Giacomelli *et al*[73] have developed a screening program using rapid immunochromatographic testing (RICT) for SARS-CoV-2 antibodies and a rapid HCV test in a single visit in three Italian cities. The results demonstrated that 2.9% of the tests were positive for HCV antibodies, and 54% of them did not know their serological status.

LT programs

During the SARS-CoV-2 pandemic, there has been an initial worldwide decline in the number of LTs for several reasons. Firstly, there has been a drastic decrease in liver donors, as well as in the availability of ICU beds for both donors and recipients. Secondly, testing organ donors for the presence of the virus is recommended, and those that are positive should be ineligible for donation. Thirdly, the evaluation of potential candidates for LT has been temporarily limited due to the lower availability of hospital resources, as well as to prevent exposure to SARS-CoV-2 in patients with advanced CLD. Finally, at the beginning of the pandemic, there was a temporary decrease in LT recommendations for patients at greater risk of worsening and mortality due to transplant delay: patients with acute liver failure, high MELD score, and HCC at upper limits of the Milan criteria[74-76].

In the United States (US), the impact on LT between March and August 2020 was evaluated using historical trends between 2016 and 2020. Within the first ten weeks of the pandemic, a dramatic decrease in new listings for LT (11%-21%), deceased donor LT (9%-13%), and living donor LT (42%-49%) was found. Besides, there was a reduction of 59% in patients included in the waiting list for LT. Despite these initial data, the mortality risk of LT waitlist candidates was not significantly different before and after COVID-19[77]. On the other hand, a national survey conducted in the US between March 24th and 31st 2020 showed that 67.7% of LT centers had stopped performing live donor LT[78]. A similar evolution in LT was observed in Italy. Considering the period of the first outbreak (March 1st–March 31st), a decrease of around 35% in LT was recorded due to the decrease in the number of donations[79]. In France, there was a 28% decrease in the number of organ donations in 2020 (543 in 2020 *vs* 752 organ donations in 2019) and a 22% decrease in the number of liver

transplantations (435 in 2020 *vs* 556 in 2019)[80], comparing two similar periods (January 1st-May 31st 2019 *vs*. January 1st-May 31st 2020). In Spain, during the first COVID-19 wave (between March 13th-April 23rd), the mean number of donors decreased from 7.2 to 1.2 per day, and the weekly mean number of LTs decreased from 23.6 to 5.7[81]. Throughout the year 2020, the number of donors and LTs reduced by 22.8% and 15.7% (1034 *vs* 1227), respectively, compared to 2019[82].

CONCLUSION

It is accepted that SARS-CoV-2 infection can cause liver damage, representing a relevant outcome that affects the prognosis of COVID-19. A direct pathogenic effect on the liver, systemic inflammation, and immune dysfunction appear to play a relevant role in this association. In this scenario, liver function tests such as AST, ALT, and bilirubin levels at admission have been related to a poor COVID-19-related prognosis, including more ICU admission requirements and deaths. Finally, we must pay attention to maintaining an adequate monitoring and follow-up of patients with liver diseases, focusing on the risk of cirrhosis decompensation and HCC screening.

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World Journal of Virology

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World J Virol 2021 November 25; 10(6): 312-325

DOI: 10.5501/wjv.v10.i6.312

ISSN 2220-3249 (online)

MINIREVIEWS

COVID-19 (SARS-CoV-2 infection) in lymphoma patients: A review

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Author contributions: Bonuomo V, Ferrarini I and Visco C designed and conceptualized the review procedure; Bonuomo V and Ferrarini I wrote the first concept of the article; Bonuomo V performed the literature research; Bonuomo V, Ferrarini I and Visco C analyzed the data and wrote the final manuscript; All authors reviewed and amended subsequent versions and discussed the clinical aspects and implications of the study.

Conflict-of-interest statement: The authors do not have any conflict of interest. No financial or non-financial benefits have been received or will be received from any party related directly or indirectly to the subject of this article.

Country/Territory of origin: Italy

Specialty type: Hematology

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

Peer-review report's scientific quality classification

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Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection now has a global resonance and represents a major threat for several patient populations. Observations from initial case series suggested that cancer patients in general might have an unfavorable outcome following coronavirus disease 2019 (COVID-19), due to their underlying conditions and cytotoxic treatments. More recently, data regarding the incidence and clinical evolution of COVID-19 in lymphomas have been reported with the aim to identify those more frequently associated with severe complications and death. Patients with lymphoma appear particularly vulnerable to SARS-CoV-2 infection, only partly because of the detrimental effects of the anti-neoplastic regimens (chemotherapy, pathway inhibitors, monoclonal antibodies) on the immune system. Here, we systematically reviewed the current literature on COVID-19 in adult patients with lymphoma, with particular emphasis on disease course and prognostic factors. We also highlighted the potential differences in COVID-19 clinical picture according to lymphoma subtype, delivered treatment for the hematological disease and its relationship on how these patients have been managed thus far.

Key Words: Lymphoma; SARS-CoV-2 infection; Hematological malignancies; COVID-19; Rituximab; Bendamustine

Core Tip: Recently, the scientific literature has been widely occupied by reports on severe acute respiratory syndrome coronavirus 2 infection. However, patients with cancer have been under-represented, and patients with lymphoma have rarely been described. The real impact of this tremendous pandemic on the life expectancy of patients with different subtypes of lymphoma is still unknown, especially in relation to chemo-, chemo-immunotherapy and/or biologic treatments. Furthermore, the

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

Received: April 21, 2021
Peer-review started: April 21, 2021
First decision: July 7, 2021
Revised: July 16, 2021
Accepted: August 9, 2021
Article in press: August 9, 2021
Published online: November 25, 2021

P-Reviewer: Dou AX, Yoshida N, Zhu F
S-Editor: Wang JL
L-Editor: Filipodia
P-Editor: Zhang YL

relationship between lymphoma patients' characteristics and the infection behavior is undescribed. With this review we pointed out what literature clarifies in the prognosis and management of patients with lymphoma during the coronavirus disease 2019 pandemic.

Citation: Bonuomo V, Ferrarini I, Dell'Eva M, Sbisà E, Krampera M, Visco C. COVID-19 (SARS-CoV-2 infection) in lymphoma patients: A review. *World J Virol* 2021; 10(6): 312-325
URL: https://www.wjgnet.com/2220-3249/full/v10/i6/312.htm
DOI: https://dx.doi.org/10.5501/wjv.v10.i6.312

INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic is a worldwide medical emergency impacting virtually all aspects of medical care. The clinical spectrum of individuals who are infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is remarkably heterogeneous, ranging from mild flu-like symptoms to life-threatening respiratory failure[1]. Mortality due to the infection is largely dependent on patients age, and the infection fatality ratio is lowest among 5–9-year-old children, with a log-linear increase by age among individuals older than 30 years. Estimated age-specific infection fatality ratios range from 0.001% in those aged 5–9-years-old to 8.29% in those aged 80+. Population age structures, heterogeneous inclusion criteria in terms of comorbidities and burdens in nursing explain some of the heterogeneity between countries in infection fatality ratio[2]. The leading cause of mortality is the acute respiratory distress syndrome. Indeed, after infecting the pneumocytes, SARS-CoV-2 triggers intracellular signaling pathways that promote the release of several proinflammatory mediators, leading to the recruitment of neutrophil and monocyte-macrophages[3-5].

Subgroups of patients with COVID-19 have been identified to be at increased risk of morbidity and mortality, including patients of older age, male sex (*vs* female) and those with comorbidities, such as hypertension, chronic lung disease, diabetes, immunodeficiency and cancer[6]. In particular, cancer patients often follow a more severe and rapid disease course, with requirement of high-level intensive care and an increased risk of COVID-19-related death[7-10]. In the first published report from the COVID-19 and Cancer Consortium, mortality among 928 analyzed adult patients with any malignancy was 13%, with 23% mortality for any admission to the hospital and 38% mortality for admission to the intensive care unit (ICU)[11]. Among 800 patients with cancer included in the United Kingdom Coronavirus Cancer Monitoring Project, reported mortality in the overall cohort was 28%[12]. A multicenter study in China of 205 patients with cancer reported mortality of 20%[13]. In the latter series, 22 patients with hematologic malignancies (HM) were included and had a mortality rate of 41%. In cancer series, hematologic patients account for 20%-25% of the total including a variable distribution of pathologies. Heterogeneous series addressing SARS-CoV-2 infection in patients with HM have been published, reflecting mortality rates ranging from 30% to 40%; however, these reports offer limited information on the characteristics of the various hematological diseases and their relationship with anticancer treatments. Patients with HM are immunocompromised, which makes them highly susceptible to severe infections. On the other hand, some authors have suggested that some patients with HM might be "protected" from severe COVID-19 morbidity due to an attenuated inflammatory response. In this review, we synthesized the current literature to illustrate the demographic, immunological and clinical features of COVID-19 infection in the specific setting of patients affected by lymphoma, a heterogeneous group of cancers arising from B or T lymphocytes and often associated with various degrees of immune dysfunction.

Lymphoma patients are at high risk of infections: patients with HM (and lymphomas) tend to carry more comorbidities than age and sex matched population, have more frequent contacts with medical systems and are often treated with immunosuppressive medications potentially blunting the antiviral immune responses. Hematologic malignancies affect the production and function of blood cells in fighting off infections[14]. Affected patients often have multiple immune dysfunctions of the innate and adaptive immune system including low immunoglobulin G serum levels (

i.e. chronic lymphocytic leukemia or other B cell neoplasms) or functionally impaired granulocytes (*i.e.* myeloid neoplasms)[15,16]. Crippled cellular and humoral immunity places these patients at risk of a diverse array of infections including COVID-19[17].

Lymphomas are a heterogeneous group of cancers broadly divided into two main histological subtypes: Hodgkin lymphoma (HL) and non-HL (NHL). HL tends to spread in a fairly orderly way from one group of lymph nodes to the next group and it affects young adults aged 20–40 years more frequently, while NHL can spread to extra nodal organs, bone marrow and spleen. The World Health Organization has recognized several forms of NHL, with diffuse large B-cell lymphoma being the most common subtype in adults[18].

Chemotherapy treatment combined with rituximab (widely available immunotherapy against B-lymphocytes) is the current standard upfront treatment for most histologies[19]. Together with lymphodepleting therapies, several intrinsic factors contribute to the typical immunosuppressive status of patients with lymphoma. Among them hypogammaglobulinemia, neutropenia and lymphopenia (both B- and T-cell related) are frequently observed features at disease presentation[20,21]. Furthermore, lymphomas are more likely to develop in patients with underlying immunosuppressive conditions, such as the human immunodeficiency virus infection, rheumatological chronic disorders, autoimmune disease or inherited congenital immune-deficiency states[22]. Lymphoma therapy has historically been based on chemotherapy variably associated with immunotherapy and radiotherapy. Moreover, in recent years, the approval of new molecules with different mechanisms of action (monoclonal antibody, small molecules, biologic agents, cell therapy) has allowed us to expand the therapeutic arsenal available for the treatment of these diseases. Among chemotherapy regimens, bendamustine is a strong inducer of T-cell immune deficiency[23]. Anti-CD20 monoclonal antibodies, such as rituximab or obinutuzumab, induce rapid depletion of more than 95% of CD20-positive mature B-cells, impairing cellular and humoral response towards new pathogens[24-26].

LITERATURE REVIEW

A review of the literature reporting on SARS-CoV-2 infection in lymphoma patients was conducted. In particular, we focused on the relationship with lymphoma characteristics and the clinical course of COVID-19 infection. An electronic search was performed to identify all studies reporting on the management of lymphoma patients during the SARS-CoV-2 pandemic. The PubMed/MEDLINE database was searched on February 6th, 2021. The search strategy was "SARS-CoV-2" OR "COVID-19" AND "lymphoma." Potential case duplicates were ruled out by analysis of demographic characteristics of the included patients and institution of origin of the reports.

PREVALENCE OF CANCER AND HM AMONG SARS-COV-2 INFECTED PEOPLE

Human infections with SARS-CoV-2 were first reported in late 2019. At the end of February 2021, the global cumulative numbers were 110.7 million cases and over 2.4 million deaths since the start of the pandemic[27]. The prevalence of cancer in patients with COVID-19 is uncertain. Studies from China reported that 1% to 2% of COVID-19 patients had cancer, and a study from the United States reported that 6% of hospitalized patients with COVID-19 had cancer. In Lombardy, Italy, they observed that 8% of the patients admitted to the ICU for COVID-19 had cancer. In a meta-analysis, the prevalence of cancer was 2% among COVID- 19 patients[28].

Reports about the prevalence of HM among COVID-19 patients are very limited. In a study from Turkey[29], 0.39% of the laboratory-confirmed COVID-19 patients had underlying blood cancer. Patients with HM were reported to be at increased risk for developing COVID-19 as compared to general population, after adjusting for age, gender, race and known COVID-19 risk factors. It has been reported that patients with cancer with different tumor types have differing susceptibility to SARS-CoV-2 infection and COVID-19 phenotypes[30]. Individualized risk tables have been generated for patients with cancer, considering age, sex and tumor subtype, reporting an increased susceptibility to SARS-CoV-2 in patients with HM.

CLINICAL MANAGEMENT AND FATALITY RATES OF PATIENTS WITH COVID-19 AND HM (INCLUDING LYMPHOMAS)

Among papers investigating the characteristics of COVID-19 infection in cancer patients, only some stratified the population by type of malignancy (reported in Table 1). He *et al*[31] conducted a cohort study at two centers in Wuhan, China, involving 128 hospitalized subjects with HM, 13 (10%) of whom developed COVID-19. There were no significant differences in baseline covariates between subjects with HM developing COVID-19 or not. Case rates for COVID-19 were similar between the two groups, but hospitalized subjects with HM were reported to suffer from more severe disease and higher case fatality rate (CFR). In a study conducted by Mehta *et al*[32] the CFR in COVID-19 patients with HM was 37%. A study from Spain[33] reported a CFR of 32% among 34 hospitalized COVID-19 patients with HM. Authors concluded that the status of underlying malignancy at the time of COVID-19 correlated with mortality, with disease activity that was directly associated with worse outcomes. Aries *et al*[34] reported a CFR as high as 40% in a small cohort including 35 patients with HM. In a study conducted by Yang *et al*[13] among 52 COVID-19 patients with solid tumors or HM, the rate of severe/critical disease was 36.5% and CFR of severe/critical patients was 57.8%. Wood *et al*[35] described 250 cases of patients with HM and COVID-19 that were enrolled into the ASH Research Collaborative COVID-19 Registry. Consistent with previous reports, patients with HM had poor outcomes, with an overall mortality rate of 28%, which increased to 42% for those patients requiring hospital-level care.

In Rüthrich *et al*[36] retrospective analysis of LEOSS study a total of 435 cancer patients with SARS-CoV-2 were included. The majority of patients were hospitalized (98%). Lymphoma and leukemia were documented for 76 (17.5%) and 48 (11%) patients, respectively. The commonest HM was NHL (16.5%). In solid tumors and HM, mortality appeared somewhat comparable, but HM were overrepresented compared to a non-COVID-19 cancer cohort from the United Kingdom, reporting a prevalence of 9.5%[30].

In the study by Passamonti *et al*[37], 536 HM patients were described. A high frequency of severe infections was reported: dyspnea occurred in 51% of patients and fever in 75% of patients. This was also evidenced by the high proportion (18%) of patients admitted to the ICU and the high number of deaths (198, 37%). Mortality of patients with HM and COVID-19 was nearly four times higher than that of the general population with COVID-19.

Similar conclusions have been reached by the Turkish study conducted by Yigenoglu *et al*[29] where COVID-19 patients with HM (n = 740) and an age, sex and comorbidity-matched cohort of COVID-19 patients without cancer (n = 740) were enrolled. NHL (30.1%), myelodysplastic syndrome (19.7%) and myeloproliferative neoplasm (15.7%) were the most common HM. The rates of severe and critical disease, hospital and ICU admission and mechanical ventilation support were significantly higher in patients with HM compared with patients without cancer. The length of hospital stay and ICU stay was similar between groups. The CFR was 13.8% in patients with HM and 6.8% in the control group. The lower CFR in this study compared with the other studies may be attributed to a high number of myeloproliferative neoplasm patients who were thought to be less immunocompromised compared with leukemia, multiple myeloma or lymphoma patients. Interestingly, they described higher use of antiviral drugs such as lopinavir/ritonavir in patients with HM.

Finally, recipients of autologous and allogeneic stem cell transplantation (HSCT) who develop COVID-19 have also been reported to have poor survival rates. The Center for International Blood and Marrow Transplant Research reported 318 HSCT recipients diagnosed with COVID-19. Disease severity was mild in 155 (49%) of 318 patients, while severe disease requiring mechanical ventilation occurred in 45 (14%), *i.e.* 28 (15%) of 184 allogeneic HSCT recipients and 17 (13%) of 134 autologous HSCT recipients. At 30 d after COVID-19 diagnosis, overall survival was 68% (95% confidence interval: 58%–77%) for recipients of allogeneic HSCT and 67% (55-78) for recipients of autologous HSCT[38]. Age 50 years or older, male sex and development of COVID-19 within 12 mo of transplantation were associated with a higher risk of mortality among allogeneic HSCT recipients.

When cancer patients are compared with control groups it appeared evident that the cancer itself constituted an independent prognostic factor in the case of COVID-19 infection. Studies investigating clinical factors associated with worse outcome in HM are summarized in Table 2.

Table 1 Characteristics of included studies

Ref.	Location	Type of malignancy included	Duration of study	Total No. of pts with HM included	Matched COVID-19 control	No. of lymphoma pts	No. of NHL pts	No. of HL pts	Mortality rate attributed to COVID-19 (Global)	Mortality rate attributed to COVID-19 (Lymphoma)	Mortality rate attributed to COVID-19 (NHL)	Mortality rate attributed to COVID-19 (HL)
Cancer studies including lymphoma pts												
Rüthrich *et al*[36], 2020	Europe	All	5 mo	435	2636	76	71	5	96/435 (22%)	20/76 (26%)	NR	NR
Lee *et al* [12], 2020	UK	All	1 mo	1044	282878	79	NR	NR	319/1044 (31%)	25/79 (31%)	NR	NR
Tian *et al* [50], 2020	China	All	9 wk	232	519	6	6	0	46/232 (20%)	2/6 (33%)	2/6 (33%)	NR
HM studies including lymphoma pts												
Aries *et al* [34], 2020	UK	HM	2 mo	35	No	8	8	0	14/35 (40%)	NR	NR	/
Biernat *et al*[51], 2020	Poland	HM	1 mo	10	No	3	3	0	7/10 (70%)	NR	NR	/
Booth *et al* [52], 2020	UK	HM	2 mo	66	No	15	15	0	34/66 (52%)	6/15 (40%)	6/15 (40%)	/
Cattaneo *et al*[42], 2021	Italy	HM	1 mo	102	101	42	40	2	40/102 (39%)	17/42 (40%)	16/40 (40%)	1/2 (50%)
Fox *et al* [53], 2020	UK	HM	1 mo	55	No	17	17	0	19/55 (35%)	7/17 (41%)	7/17 (41%)	/
Garcìa-Suàrez *et al* [54], 2020	Spain	HM	8 wk	697	No	220	187	33	230/697 (33%)	68/220 (31%)	59/187 (32%)	9/33 (27%)
Infante *et al*[55], 2020	Spain	HM	1 mo	41	No	15	14	1	15/41 (37%)	NR	NR	NR
Lattenist *et al*[56], 2021	Belgium	HM	2 mo	12	No	2	2	0	6/12 (50%)	2/2 (100%)	2/2 (100%)	/
Malard *et al*[57], 2020	France	HM	1 mo	25	No	7	7	0	10/25 (40%)	0/7 (0%)	0/7 (0%)	/
Martín-Moro *et al* [33], 2020	Spain	HM	5 wk	34	No	6	5	1	11/34 (32%)	0/6 (0%)	0/5 (0%)	0/1 (0%)
Mehta *et al* [32], 2020	USA	HM	3 wk	54	No	20	15	5	20/54 (37%)	8/20 (40%)	5/15 (33%)	3/5 (60%)
Passamonti *et al*[37], 2020	Italy	HM	12 wk	536	No	170	153	17	198/536 (37%)	65/170 (38%)	62/153 (40%)	3/17 (18%)
Sanchez-Pina *et al* [58], 2020	Spain	HM	1 mo	39	53	12	NR	NR	14/39 (36%)	2/12 (14%)	NR	NR
van Doesum *et al*[59], 2020	Europe	HM	9 wk	59	No	17	15	2	NR	NR	NR	NR
Yigenoglu *et al*[29], 2021	Turkey	HM	15 wk	740	188897	250	223	27	103/740 (14%)	28/250 (11%)	24/223 (11%)	4/27 (14%)
Wood *et al* [35], 2020	Worldwide	HM	3 mo	250	No	79	68	11	70/250 (28%)	20/79 (25%)	16/68 (24%)	4/11 (36%)
Lymphoma studies												
Regalado-Artamendi	Spain	Lymphoma	12 wk	177	No	177	158	9	61/177 (29%)	61/177 (29%)	NR	NR

et al[40], 2021												
Lamure *et al*[39], 2020	France	Lymphoma	8 wk	89	No	89	84	5	30/85 (34%)	30/85 (35%)	29/84 (34%)	1/5 (20%)
Laurenge *et al*[60], 2021	France	PCNSL	2 mo	13	No	13	13	/	3/13 (23%)	3/13 (23%)	3/13 (23%)	

COVID-19: Coronavirus disease 2019; HM: Hematologic malignancy; HL: Hodgkin lymphoma; NHL: Non-Hodgkin lymphoma; NR: Not reported; PCNSL: Primary central nervous system lymphoma; pts: Patients; UK: United Kingdom; USA: United States of America.

Table 2 Prognostic factors associated with survival in lymphoma series

Ref.	Details on study cohort	Univariate analysis for predictors of death	Multivariate analysis for predictors of death
Regalado-Artamendi *et al*[40], 2021	Lymphoma patients	Age ≥ 70 yr	Age ≥ 70 yr
		Comorbidities	Comorbidities
		CURB65 ≥ 3	CURB ≥ 2
		Low platelet count	Active disease
		Low hemoglobin level	
		High D-dimer	
		C-reactive protein >10 mg/dL	
		LDH > 300 U/L	
		Active disease[1] (reference to CR)	
		DLBCL histology (reference to FL)	
		High-risk lymphoma[2] (reference to low risk)	
Lamure *et al*[39], 2020	Hospitalized lymphoma patients	Age ≥ 70 yr	Age ≥ 70 yr
		Hypertension	Active disease
		Previous cancer	
		Bendamustine treatment	
		Active disease	

[1]Partial response or progression.

[2]High risk according to prognostic index at diagnosis. CR: Complete response; CURB65: Confusion, urea concentration, respiratory rate, blood pressure and age > 65; DLBCL: Diffuse large B cell lymphoma; FL: Follicular lymphoma; LDH: Lactate dehydrogenase.

LYMPHOMA SERIES AND CASE REPORTS, CLINICAL FEATURES AND FATALITY RATES

Lymphoma patients represented a small proportion of the entire cancer series, also reflecting the relative prevalence of this disease compared to solid tumors. Figure 1 resumed the number of lymphoma patients described all over the world in the largest HM studies. However, subset data from and disease-specific cohorts are emerging. Two recently published series focused specifically on patients with lymphoma. The first report was from France where Lamure *et al*[39] described clinical characteristics and outcomes of 89 adult patients with lymphoma hospitalized for COVID-19 in 12 hospitals during the first pandemic wave. Overall, reported 1 mo overall survival was 71%. The most common symptoms at presentation were dyspnea (65%), cough (60%), fever (48%) and diarrhea (24%). The median duration of symptoms before admission was 6 d. Lymphopenia was observed in 66% of patients. During hospitalization, 25 patients (28%) were admitted to the ICU. This CFR was documented despite a significant fraction of patients had received the best available cures against SARS-CoV-

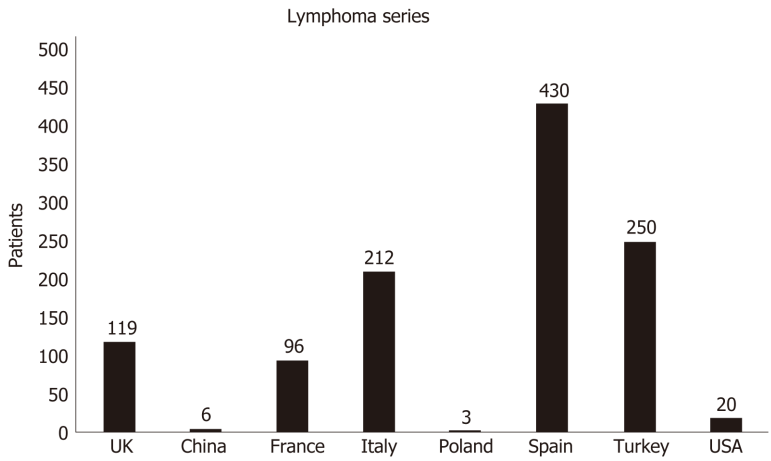

Figure 1 Number of lymphoma patients described all over the world in largest hematologic malignancy studies. UK: United Kingdom; USA: United States of America.

2: chloroquine and hydroxychloroquine (11 patients) or antiviral drugs combinations (10 patients). Six patients had received treatment for cytokine shock (tocilizumab, anakinra and eculizumab for two patients each). Seventeen patients (19%) developed a documented coinfection and three an (3%) acute pulmonary embolism.

The second series from Regalado-Artamendi *et al*[40] collected 177 cases affected by COVID-19 in Spain. The median incubation time was again 5 d, with fever and cough as the most frequent symptoms at presentation; the presence of dyspnea at presentation was related to CFR. More than 85% of patients required hospital admission, with 9% admitted to the ICU and an overall mortality rate of 34.5%.

Numerous case reports of patients affected by lymphoma and COVID-19 have been reported and summarized in Table 3. These cases have been published over the last 12 mo, witnessing the widespread interest of the scientific community and the difficulties encountered in the management of these patients. Several lymphoma histotypes are described, with disparate outcomes.

PROGNOSTIC FACTORS ASSOCIATED WITH SURVIVAL IN PATIENTS WITH LYMPHOMA

As previously mentioned, in most of the cancer series including HM, male sex, active disease and advanced age were associated with higher CFR attributed to COVID-19 [30,36,41,42]. Passamonti *et al*[37] observed that overall survival in patients affected by HM and COVID-19 was independently predicted by age, type of malignancy, disease status and the severity of COVID-19. NHL (with no mention of histological subtype), acute myeloid leukemia and plasma cell neoplasms, together with progressive disease status, were independently predictive of poor outcomes. Among patients with NHLs, 4 (31%) of 13 patients on rituximab maintenance, 27 (47%) of 57 on active treatment with rituximab–chemotherapy and 8 (44%) of 18 on chemotherapy alone died. No association between overall survival and time since HM diagnosis or last treatment was described. In Lamure *et al*[39] series from France, which specifically focused on hospital admitted lymphoma patients with a median follow-up of 33 d from admission, 30 d overall survival was 71%, (95% confidence interval: 62%-81%). Factors independently associated with death were advanced age (> 70 years) and relapsed/refractory lymphoma. Interestingly, treatment with bendamustine (n = 9) was associated with a higher risk of death. No significant difference in the rate of death was described for patients with different lymphoma histology.

In the Regalado-Artamendi *et al*[40] series from Spain, also specifically addressing lymphoma patients, the overall mortality rate was 34.5%. Age > 70 years, heart disease, chronic kidney disease and confusion, urea concentration, respiratory rate, blood pressure and age > 65 score ≥ 2 were statistically significant mortality predictors, resembling previous reports in cancer patients. Among the variables related to lymphoma, the presence of active disease was a strong predictor of death. However, active treatment, the number of previous lines or type of treatment did not modify mortality risk. Quite surprisingly but confirming previous reports, the use of

Table 3 Case reports and case series of coronavirus disease 2019 infection in lymphoma patients

Ref.	No. of patients described	Sex	Age	Details on lymphoma diagnosis	Details on lymphoma treatment	Outcome of COVID-19 infection	Global outcome
Li *et al*[61], 2020	1	M	26 yr	PMLBCL	R-DA-EPOCH	Recovered	Alive
Tepasse *et al*[62], 2020	2	M	65 yr	DLBCL with CNS relapse	R-DeVIC	Not recovered	Dead
		M	66 yr	MCL in CR	Rituximab maintenance	Not recovered	Dead
O'Kelly *et al*[63], 2020	1			cHL second relapse	Pembrolizumab	Recovered	Alive
Baang *et al*[64], 2021	1	M	60 yr	Relapsed/Refractory MCL	R-CHOP	Recovered	Alive
Moore *et al*[65], 2020	1	F	63 yr	NHL	Obinotuzumab maintenance	Recovered	Alive
Alsuliman *et al* [66], 2020	2	M	71 yr	MCL relapsed	Ibrutinib	Recovered	Alive
		M	NR	MCL relapsed	Ibrutinib	Recovered	Alive
Hoffmann *et al* [67], 2021	3	F	68 yr	DLBCL, FL	R-CHOP	Recovered	Alive
		M	60 yr	DLBCL, FL	R-ICE	Not recovered	Dead
		M	75 yr	DLBCL	R-CHOP	Not recovered	Dead
Yonal-hindilerden *et al*[68], 2021	1	F	55 yr	Relapsed/Refractory cHL	Brentuximab	Not recovered	Dead
Fujii *et al*[69], 2021	1	M	43 yr	cHL	A + AVD	Recovered	Alive
Kamel, 2021	1	M	58 yr	ALCL	None	Not recovered	Dead
Santana *et al*[70], 2021	1	F	47 yr	FL	Rituximab maintenance	Recovered	Alive
Velier *et al*[71], 2021	1	F	61 yr	WM	None	Recovered	Dead
Pelcovits *et al*[72], 2021	1	M	43 yr	High Grade B Cell Lymphoma, NOS	R-CODOX-M/IVAC	Recovered	Alive
Otsuka *et al*[73], 2020	1	M	56 yr	MCL	R-hyper CVAD/MA	Not recovered	Dead

A + AVD: Brentuximab vedotin, dacarbazine, doxorubicin, vinblastine; ALCL: Anaplastic large-cell lymphoma; cHL: Classic Hodgkin lymphoma; CNS: Cerebral nervous system; COVID-19: Coronavirus disease 2019; CR: Complete remission; DLBCL: Diffuse large B-cell lymphoma; F: Female; FL: Follicular lymphoma; M: Male; MCL: Mantle cell lymphoma; NHL: Non-Hodgkin lymphoma; NOS: Not otherwise specified; PMLBCL: Primary mediastinal large B-cell lymphoma; R-CHOP: Rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone; R-CODOX-M/IVAC: Rituximab, cyclophosphamide, vincristine, doxorubicin and methotrexate alternating with ifosfamide, etoposide and cytarabine; R-DA-EPOCH: Dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin and rituximab; R-DeVIC: Rituximab, dexamethasone, etoposide, ifosfamide carboplatin; R-hyper CVAD/MA: Rituximab/cyclophosphamide/vincristine sulfate/doxorubicin and hydrochloride/dexamethasone/methotrexate/cytarabine; R-ICE: Rituximab, ifosfamide, carboplatin and etoposide; WM: Waldenstrom macroglobulinemia.

monoclonal antibodies (*i.e.* rituximab) was not associated with impaired survival for lymphoma patients. The detrimental effect of therapy based on bendamustine was not independently confirmed in this study.

A subanalysis in regard to lymphoma histology observed that aggressive tumors (*i.e.* diffuse large B-cell lymphoma) were associated with significantly worse overall survival compared with indolent forms (*i.e.* follicular lymphoma; 50% *vs* 80%, P = 0.0028). However, the study was not able to demonstrate clear differences between the various lymphoma histologies and therapeutic schemes; these variables were grouped into categories that could have limited the statistical power of this subanalysis. Finally, the persistence of SARS-CoV-2-positive PCR after week 6 was significantly associated with mortality. In the previously cited series describing the outcome of transplanted patients, the subgroup of patients with lymphoma (among other HM) was associated with a higher risk of death compared with plasma cell disorder or myeloma in

autologous HSCT recipients[38].

REPORTS OF SPONTANEOUS REMISSIONS IN PATIENTS WITH LYMPHOMAS

Few cases along the literature indicate that some patients may benefit of lymphoma remission when infected by COVID-19. In one case, a dramatic transient reduction in plasmatic Epstein–Barr virus (EBV)-DNA viral copies during COVID-19 pneumonia and resolution of lymphoma relapse were reported[43]. In another report, a 61-year-old man with EBV-positive classical HL with progressive lymphadenopathy and weight loss was admitted with breathlessness and wheezing and was diagnosed with PCR-positive SARS-CoV-2 pneumonia. No corticosteroid or immunochemotherapy was administered. Four months later, palpable lymphadenopathy had reduced, and an interim positron emission tomography–computed tomography scan revealed widespread resolution of the lymphadenopathy. The EBV viral PCR had also fallen [44]. The authors hypothesized that the SARS-CoV-2 infection triggered an antitumor immune response, as it has been described with other infections in the context of high-grade NHL. It is noteworthy that in both cases EBV reactivation was present.

A 61-year-old patient affected from follicular lymphoma also noted a shrinkage of a para-aortic lymph nodal lesion compared to baseline during SARS-CoV-2 infection [45]. Finally, complete spontaneous remission of diffuse large B-cell lymphoma of the maxillary sinus after concurrent SARS-CoV-2 infection was reported, with the patient's facial swelling resolving during the hospitalization[46].

Since these reports represent anecdotal observations, further data are needed to address or confirm the relationship between the virus and lymphoma subtypes as well its behavior in parallel to anti-neoplastic response.

CONCLUSION

In our opinion, our search for lymphoma patients among other cancer in the recent COVID-19 literature may deliver some important messages for the scientific community. The analysis we performed reveals that there is an increased risk of COVID-19 related serious events (ICU admission, mechanical ventilation support or death) in patients with lymphomas as compared to COVID-19 patients without cancer and confirms the high vulnerability of such patients in the current pandemic. Overall, among the HM series, lymphoma represented the commonest malignancy. In lymphoma patients COVID-19 presentation symptoms occurred a median of 5 to 6 d before hospitalization, being represented by fever, cough and dyspnea. The mortality rate, taking into account the different characteristics of the populations studied, and different lymphoma subtypes was relatively high, attesting at approximately 30% after 1-2 mo of follow-up, at least in hospitalized patients.

In a meta-analysis of hematologic malignancies and COVID-19 that incorporated data from more than 3000 patients, pooled risk of death for lymphomas was 32%[28].

Active disease at COVID-19 infection presentation or lymphoma status as progressive disease appeared to be among the strongest predictors of early death. Among histotypes, no definitive conclusions can be drawn, while the use of bendamustine (but not anti-CD20 antibodies) has been associated with increased risk of death in at least one study. Published results indicate that the start of treatment should not be delayed given that active treatment has not been associated to increased risk of mortality. Instead, achieving disease remission could lead to better outcomes. Currently, little is known about specific phenotypic and/or functional T cell changes associated with symptomatic and asymptomatic SARS-CoV-2 infection, as in patients treated with immune checkpoint inhibitors. In cancer patients[47,48], treatment with immune checkpoint inhibitors did not increase risk of adverse events compared to standard chemotherapy and did not seem to increase COVID-19 susceptibility. However, no data are reported on patients with lymphoma.

With several vaccines available, it would be extremely important to protect frail categories as soon as possible. The humoral response of patients with lymphoma to COVID-19 vaccines has been investigated by several groups[49]. Altogether, these data suggest that the humoral response in lymphoma patients is impaired as compared to other HM, especially after treatment with anti-CD20 containing therapies. Different vaccination strategies are therefore warranted for lymphoma patients. Longer term

clinical follow-up and biological monitoring of immune responses is warranted to explore the impact of lymphoma and its treatment on the immunity and prolonged outcome of patients with COVID-19 infection.

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World Journal of Virology

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World J Virol 2021 November 25; 10(6): 326-328

DOI: 10.5501/wjv.v10.i6.326

ISSN 2220-3249 (online)

LETTER TO THE EDITOR

Evaluation of an asymptomatic COVID-19 patient post-surgery with chest radiography: A surgeon's dilemma

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Author contributions: Govil G performed the study conception and design, and manuscript writing and revision; Tomar L contributed to the conception and revision of the manuscript into its final form; Dhawan P performed manuscript revision; all authors read and approved the final manuscript.

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

Country/Territory of origin: India

Specialty type: Virology

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

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

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Abstract

Routine chest radiography is not a requirement in post-surgery cardiac bypass patients. However, the safety of abandoning routine chest radiographs in critically ill patients remains uncertain. Surgery in an asymptomatic coronavirus disease 2019 (COVID-19) patient presents additional challenges in postoperative management. Chest radiography remains a valuable tool for assessment of all patients, even a stable one. Management of surgical patients as an emergency in an asymptomatic COVID-19 case remains a surgeon's dilemma.

Key Words: COVID-19; Cardiac surgery; Radiography; Critical care; Chest radiography; Intensive care; Postoperative

Core Tip: Spallanzani guidelines consider chest radiographs as a valuable tool for initial assessment and follow-up of coronavirus disease 2019 patients, even in stable asymptomatic patients. A high index of suspicion will reduce the risk of high fatal postoperative outcomes.

Citation: Govil G, Tomar L, Dhawan P. Evaluation of an asymptomatic COVID-19 patient post-surgery with chest radiography: A surgeon's dilemma. *World J Virol* 2021; 10(6): 326-328
URL: https://www.wjgnet.com/2220-3249/full/v10/i6/326.htm
DOI: https://dx.doi.org/10.5501/wjv.v10.i6.326

Received: May 27, 2021
Peer-review started: May 27, 2021
First decision: July 31, 2021
Revised: August 12, 2021
Accepted: November 14, 2021
Article in press: November 14, 2021
Published online: November 25, 2021

P-Reviewer: Watanabe A
S-Editor: Fan JR
L-Editor: A
P-Editor: Fan JR

TO THE EDITOR

We enjoyed reading the recently published article by Omar *et al*[1] about their observation on the necessity of chest radiographs (CXRs) in postoperative cardiac bypass graft cases in coronavirus disease 2019 (COVID-19)-positive patients. Although their series of patients with favourable post-surgery outcomes was small, their courage and willingness to help in the hour of need with the required COVID-19 protocols was commendable.

We agree with most of the content of the article. However, we would like to put forth more insights on the use of CXRs when dealing with surgical patients, especially an asymptomatic COVID-19 patient.

Omar *et al*[1] rightly indicated that routine CXRs are not a requirement in post-surgery cardiac bypass patients. This aspect has been researched and concluded by other authors in larger study groups. Rao *et al*[2] recommended performing CXRs only when clinically indicated, according to their finding from a study of 300 adult cardiac surgical patients showing satisfactory recovery. The systematic review and meta-analysis by Ganapathy *et al*[3] concluded that a restrictive CXR strategy in the intensive care unit does not cause harm; however, they cautioned that the safety of abandoning routine CXRs in critically ill patients remains uncertain. Tolsma *et al*[4] studied 1102 patients and concluded that selective CXR was an effective and safe approach once clear indications are defined. Porter *et al*[5] studied thoracic surgery patients and concluded that routine postoperative CXR in immediate intensive care management and later after final chest tube removal had a limited impact on clinical care.

Barkhordari *et al*[6] studied 25 asymptomatic COVID-19 patients undergoing emergent or urgent cardiac surgery, of which 84% received a cardiac bypass graft. They concluded that the majority of the patients had comparable early postoperative respiratory outcomes to their matched cohort of pre-COVID-19 patients. However, an intensive care unit readmission fared extremely poorly. They emphasised a lung-protective strategy during anaesthesia by maintaining appropriate tidal volumes with adjustments of ventilatory parameters based on perioperative acid-base and hemodynamic analyses.

Omar *et al*[1] reported on three asymptomatic cases with a mild grade of COVID-19 infection. Surgeries during the COVID-19 pandemic represent significant challenges for the patient and health care workers. There is a need for close monitoring of evaluation parameters or alarm signs in immediate postoperative management. The CXR utility for initial assessment and follow-up of COVID-19 patients is a valuable tool, even in stable patients as highlighted by the Spallanzani guidelines[7]. In COVID-19 infection, chest computed tomography in the postoperative period also needs judicious consideration based on the clinical distress symptoms to alert the surgeon of the possibility of the progression of respiratory involvement. A high index of suspicion will reduce the risk of fatal outcomes[8]. Abate *et al*[9], in their systematic review and meta-analysis on 2947 patients, revealed that perioperative mortality was 29% amongst the patients posted for emergency surgery. They also analysed hypertension as one of the most common comorbidities and pulmonary complications as one of the most common perioperative complications among surgical patients.

The developing strategies for management of asymptomatic COVID-19 patients during emergency surgery remains a surgeon's dilemma. An asymptomatic COVID-19 patient may deteriorate abruptly and collapse quickly. A surgeon should maintain focus on decreasing perioperative mortality, preventing transmission of infection to health care workers, avoiding undertreatment, and adopting a less risky approach by undertaking routine CXR evaluation for immediate postoperative management. Of note, dyspnoea may present with COVID-19 pneumonia as well as myocardial infarction or acute decompensated heart failure. The surgeon needs to adapt constantly to the challenges of evolving clinical presentations, developing virus mutations and changing transmissibility of the COVID-19 virus to ensure patient safety.

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World Journal of Virology

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

World J Virol 2021 November 25; 10(6): 329-331

DOI: 10.5501/wjv.v10.i6.329

ISSN 2220-3249 (online)

LETTER TO THE EDITOR

Effects of COVID-19 in lymphoid malignancies

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Author contributions: Öner Özdemir did all the work.

Conflict-of-interest statement: None.

Country/Territory of origin: Turkey

Specialty type: Virology

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

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): D
Grade E (Poor): 0

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Abstract

I will have a couple of comments on the issues elaborated in the article titled as 'Impact of COVID-19 in patients with lymphoid malignancies'. First, the author did not emphasize and overlook the prolonged persistence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) RNA in coronavirus disease 2019 (COVID-19) patients with hematological malignancies. Second, the rise of a chronic lymphoid leukemia clone in COVID-19 was not mentioned by the authors. Third, achieving a complete remission in asymptomatic COVID-19 patients with follicular lymphoma in partial remission after bendamustine-based therapy is not specific to this lymphoma subtype. Fourth, follicular lymphoma does not always undergo complete remission with SARS-CoV-2 infection. Our aim is to help the authors to discuss and clarify these issues a little more in COVID-19 patients with hematological malignancies.

Key Words: COVID-19; Tumor; SARS-CoV-2; Lymphoid malignancy

Core Tip: I have several comments on the article titled as 'Impact of COVID-19 in patients with lymphoid malignancies'. The author did not emphasize a couple of issues related to the effects of severe acute respiratory syndrome coronavirus 2 infection in various lymphoid malignancies. This letter helps to clarify these issues more in coronavirus disease 2019 (COVID-19) patients with hematological malignancies.

Citation: Özdemir Ö. Effects of COVID-19 in lymphoid malignancies. *World J Virol* 2021; 10(6): 329-331

URL: https://www.wjgnet.com/2220-3249/full/v10/i6/329.htm

DOI: https://dx.doi.org/10.5501/wjv.v10.i6.329

Received: June 16, 2021
Peer-review started: June 16, 2021
First decision: July 31, 2021
Revised: August 4, 2021
Accepted: November 14, 2021
Article in press: November 14, 2021
Published online: November 25, 2021

P-Reviewer: Covino M, Ribeiro IB, Watanabe A
S-Editor: Fan JR
L-Editor: Wang TQ
P-Editor: Fan JR

TO THE EDITOR

I have read the original article by Riches[1] entitled 'Impact of COVID-19 in patients with lymphoid malignancies' with great interest[1].

I will have a couple of comments on the issues elaborated in their article.

First, the author did not emphasize and overlook the prolonged persistence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) RNA in coronavirus disease 2019 (COVID-19) patients with hematological malignancies. The author just slightly touched upon within a sentence consisting of a couple of words (the persistence of a positive polymerase chain reaction for SARS-CoV-2) under the section of 'Impact of COVID-19 by Lymphoma Subtype'. However, I think that this is a huge and important problem itself and its management needs to be discussed especially in this kind of article. Here, I give some exemplary articles from the recent literature such as in King's College Hospital experience[2], Karataş *et al*[3]'s, and Perini *et al*[4]'s studies.

Second, Largeaud *et al*[5] reported 'major rise of a chronic lymphoid leukemia clone during the course of COVID-19'. This aspect of CLL and COVID-19 disease should also be discussed by the author.

Third, the author discusses achieving a complete remission in asymptomatic COVID-19 patients with follicular lymphoma in partial remission after bendamustine-based therapy. When we look at the literature, this is not just specific to follicular lymphoma, but other hematological malignancies as well, such as in diffuse large B-cell lymphoma and Hodgkin lymphoma after concurrent other and SARS-CoV-2 infections, respectively[6]. Also, just a perfect article titled as 'complete remission of follicular lymphoma after SARS-CoV-2 infection: From the "flare phenomenon" to the "abscopal effect"' is reported by Sollini *et al*[7]. This issue should also further be elucidated.

Fourth, follicular lymphoma does not always undergo complete remission with SARS-CoV-2 infection, reported by Tafti *et al*[8] and Wright *et al*[9]. Indeed, in some malignancy patients, SARS-CoV-2 infection persisted, and COVID-19 pneumonia and the multimicrobial superinfection developed. Even, convalescent plasma needed to be utilized in the patient[9].

The authors did not emphasize a couple of issues related to the effects of SARS-CoV-2 infection in various lymphoid malignancies. Our aim is to help to clarify these issues a little more in COVID-19 patients with hematological malignancies.

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