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Contents

Bimonthly Volume 12 Number 4 July 20, 2022

OPINION REVIEW

REVIEW

MINIREVIEWS

ORIGINAL ARTICLE

Prospective Study

SYSTEMATIC REVIEWS

World Journal of Methodology

Bimonthly Volume 12 Number 4 July 20, 2022

Contents

META-ANALYSIS

World Journal of Methodology

Bimonthly Volume 12 Number 4 July 20, 2022

Contents

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OPINION REVIEW

Laparoscopic bilateral inguinal hernia repair: Should it be the preferred technique?

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Abstract

Inguinal hernias are amongst the most common conditions requiring general surgical intervention. For decades, the preferred approach was the open repair. As laparoscopy became more popular and available and more surgeons became familiarized with this modality, laparoscopic inguinal hernia repair became an alternative. The aim of this study is to assess the effectiveness of laparoscopic inguinal repair, with a focus on bilateral inguinal hernias. Initial reports have shown promising clinical outcomes compared to those of conventional repair of bilateral hernias. However, there are only a few studies concerning laparoscopic repair of bilateral hernias. It is yet to be proven that laparoscopy is the "gold standard" in the treatment of bilateral inguinal hernias. So far, the choice of an inguinal hernia repair technique has been up to each surgeon, depending on their expertise and available resources after taking into consideration each patient's needs.

Key Words: Bilateral inguinal hernia; Laparoscopic repair; Open repair: Gold standard; Chronic pain; Recurrence

Core Tip: Laparoscopic repair of bilateral inguinal hernias has become a common procedure over the past few years. It is associated with less pain and faster return to daily life compared to the open repair. As yet, there is little evidence to sufficiently support that it should be the preferred technique, as it depends on each surgeon to choose the repair technique that they will use.

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INTRODUCTION

Inguinal hernias are amongst the most frequent clinical manifestations of a general surgery department. Therefore, surgical procedures, both elective and emergent, are in most cases necessary to relieve the symptoms caused by hernias. Incidence of inguinal hernias is greater in patients older than 50 years of age, although they are also common in young children and infants. The vast majority of patients are male[1,2]. Bilateral hernias represent approximately 8% to 30% of inguinal hernias[3].

Mesh repair, such as the Lichtenstein or laparoscopic mesh repair approach, should be considered first by a surgeon. When considering non-mesh techniques, the Shouldice repair should be the primary choice[4]. Currently, open mesh repair remains the most widely used technique[5]. The European Hernia Society recommends laparoscopic repair for recurrent inguinal hernias. Regarding unilateral hernias, the choice between an open or laparoscopic approach depends on each surgeon and their expertise, as a surgeon needs to perform 50 to 100 repairs to master the laparoscopic repair technique [5]. When it comes to bilateral inguinal hernias, there is no official recommendation; however the European Hernia Society highlights that laparoscopic repair of bilateral hernias is associated with better short-term results without undermining long-term results[4,6]. This is stated as "self-evident" in the 2018 HerniaSurge guidelines, as a laparoscopic operation of two inguinal hernias through the same three incisions is considered superior in terms of recovery, chronic pain and cost-effectiveness[5]. Time to recovery and postoperative pain are considered to be less in laparoscopic repair due to less surgical trauma as it promotes diminished acute inflammatory postoperative response, proven by smaller quantities of cytokines[7].

The purpose of this study was to evaluate the effectiveness of laparoscopic repair techniques in bilateral inguinal hernias and to examine whether laparoscopic repair is superior compared to open repair based on the existing literature.

SEARCH OF THE LITERATURE

We conducted a thorough search of the literature using PubMed, the Scopus Elsevier Database and Cochrane Database. The search terms we used were: "bilateral hernias", "inguinal hernias", "laparoscopic hernia repair", "laparoscopic *vs* open hernia repair", "postoperative pain", "chronic groin pain", "cost-effectiveness", "quality-of-life" and "recovery". We collected the international guidelines regarding hernia repair issued by the European Hernia Society and HerniaSurge Group in order to review the official recommendations.

As there was no official recommendation on using laparoscopic repair in bilateral inguinal hernias as the "gold standard," our main goal was to review the available literature to examine whether there is evidence supporting this assumption. We reviewed all available literature on this subject, with emphasis on prospective randomized trials. We included data from six prospective randomized studies regarding bilateral hernias (Table 1) and from one prospective randomized study, which focused on unilateral hernias but was the first to suggest beneficial results of laparoscopic repair on bilateral hernias. We also retrieved data from one prospective randomized trial that compared different techniques of laparoscopic repair. We reviewed comparative studies, meta-analysis and one large-scale retrospective study. The draft of this manuscript was written on Microsoft Word v.16 of Microsoft Corporation.

LAPAROSCOPIC HERNIA REPAIR

Since the introduction of laparoscopic repair techniques, there has been a debate regarding the superiority of laparoscopic over open inguinal hernia repair. Initial analysis has shown that laparoscopic repair is at least not inferior compared to the open approach in terms of operative time, postoperative pain, recovery and hospital stay[8]. The main factors used to compare the two approaches are immediate postoperative pain and pain following the months after surgery as well as mean postoperative recovery time to daily activities[9]. As there has been tremendous progress in laparoscopic surgery in the past decades, laparoscopic hernia repair techniques are now becoming widely available to surgeons, and there is a belief that these techniques may supersede open repair procedures.

Table 1 Prospective randomized trials regarding bilateral hernias

Ref.	Journal	Title of study	Compared techniques	Patients	Subject
Sarli *et al* [20], 2001	*Surg Laparosc Endosc Percutan Tech*	Simultaneous repair of bilateral inguinal hernias: A prospective, randomized study of open, tension-free *vs* laparoscopic approach	TAPP *vs* Lichtenstein	43 (20 *vs* 23)	Surgical procedure, postoperative pain and course, follow-up, cost analysis
Mahon *et al*[21], 2003	*Surg Endosc*	Prospective randomized trial of laparoscopic (transabdominal preperitoneal) *vs* open (mesh) repair for bilateral and recurrent inguinal hernia	TAPP *vs* Lichtenstein	120 (60 *vs* 60)	Surgical procedure, postoperative pain and course, recovery
Ielpo *et al* [22], 2018	*Am J Surg*	A prospective randomized study comparing laparoscopic TAPP *vs* Lichtenstein repair for bilateral inguinal hernias	TAPP *vs* Lichtenstein	134 (61 *vs* 73)	Surgical procedure, postoperative course, recovery, quality of life, chronic pain
Bignell *et al*[23], 2012	*Hernia*	Prospective randomized trial of laparoscopic (TAPP) *vs* open (mesh) repair for bilateral and recurrent inguinal hernia: incidence of chronic groin pain and impact on quality of life: Results of 10-yr follow-up	TAPP *vs* Lichtenstein	120 (60 *vs* 60)	Chronic groin pain, quality of life
Hynes *et al*[24], 2006	*J Am Coll Surg*	Cost effectiveness of laparoscopic *vs* open mesh hernia operation: Results of a department of veterans affairs randomized clinical trial	All laparoscopic *vs* all open	1395 (687 *vs* 708)	Quality of life, cost-effectiveness
Ielpo *et al* [25], 2018	*Ann Surg*	Cost-effectiveness of randomized study of laparoscopic *vs* open bilateral inguinal hernia repair	TAPP *vs* Lichtenstein	165 (81 *vs* 84)	Quality of life, cost-effectiveness, cost analysis

TAPP: Transabdominal preperitoneal.

LAPAROSCOPIC REPAIR TECHNIQUES

Laparoscopic inguinal hernia repair may be conducted using two different techniques the transabdominal preperitoneal procedure (TAPP) and the totally extraperitoneal procedure (TEP). These approaches may differ in terms of access but share the same concepts of laparoscopic surgery. So far, they have shown similar outcomes in terms of recovery, hospital stay, chronic pain and quality of life [10]. TAPP, although it is easier to learn and perform, has a longer operating time and greater incidence of postoperative pain, while TEP is associated with a greater incidence of seroma formation. The differences between the two approaches are not significant, thus the techniques are comparable. It is reported that the risk for seroma and hematoma formation is also comparable regarding TAPP, TEP and the open repair[11]. The cost for both laparoscopic procedures is similar[10,12].

Since the first studies regarding laparoscopic hernia repair techniques were published, these techniques have progressed. Newer lightweight meshes are associated with less pain and a lower recurrence rate, in contrast to outdated heavyweight meshes[13]. Mesh fixation techniques have also undergone changes in the past few years. Tack fixation while widely used, is associated with considerable postoperative pain due to the presence of a foreign body in the inguinal region. In recent years, titanium tacks have gradually been replaced by absorbable tacks, which cause less pain[14]. Transfacial suture fixation and fibrin glue fixation are new techniques associated with significantly less pain compared to the use of tacks[15,16]. The technique shown to cause minimal pain, both postoperatively and long-term, is the use of a lightweight mesh fixed using fibrin glue[17,18]. We must note that in the totally extraperitoneal procedure, mesh fixation is not a prerequisite, and it can be avoided without putting the effectiveness of the procedure in danger[19].

DO SHORT-TERM RESULTS INDICATE LAPAROSCOPIC REPAIR OF BILATERAL INGUINAL HERNIAS AS A BETTER OPTION?

There are three randomized prospective trials in the literature that compare laparoscopic to open repair of bilateral inguinal hernias. Sarli *et al*[20] published the first prospective randomized control trial, which included 43 patients, comparing open mesh repair to laparoscopic repair of bilateral inguinal hernias. In their study, the Lichtenstein procedure was compared to the TAPP, and factors such as operating time, complications, postoperative pain, time to recovery and cost-effectiveness were analyzed, with a follow-up of up to 3 years postoperatively. Despite a higher cost, laparoscopic repair was associated with faster recovery and less pain in the immediate postoperative period, while complications, days of hospitalization and recurrence rates were similar in both groups[20].

These first results were subsequently supported by the randomized control trial of Mahon *et al*[21]. In this study, a total of 120 patients were included. The endpoint of this study was the superiority of TAPP over the open repair for bilateral hernias, in terms of postoperative pain, days of hospitalization and time to recovery[21]. Ielpo *et al*[22] published their randomized control trial in 2018, comparing TAPP with the open repair for bilateral inguinal hernias. In their study, a total of 134 patients were included over a 2-year span. Their results supported those of prior randomized controlled trials, in terms of beneficial short-term results, such as recovery, postoperative pain and complications[22].

Clinical outcomes of laparoscopic surgery outperformed those of open repair and supported the concept of establishing laparoscopic repair in bilateral inguinal hernias as the "gold standard," regardless of the technique performed (as TAPP and TEP are associated with similar outcomes)[12,20-22].

IS THERE SUFFICIENT EVIDENCE OF LONG-TERM SUPERIORITY OF THE METHOD?

Chronic pain, quality of life and recurrence rates are the most important factors to evaluate long-term superiority. In the study of Ielpo *et al*[22], chronic pain and long-term quality of life are under investigation, and it is one of the two published randomized controlled trials regarding chronic pain, along with the 2012 study of Bignell *et al*[23]. The results of the study by Ielpo *et al*[22] indicated that patients undergoing laparoscopic repair had less postoperative pain, fewer complications and, more importantly, less chronic pain, but there was no statistically significant difference regarding the long-term quality of life.

Chronic groin pain is one of the factors indicative of long-term success of the method. The existing literature suggests that laparoscopic repair is superior in terms of short-term clinical outcomes but, so far, has failed to provide adequate evidence of superiority in the years following surgery. Incidence of chronic pain in the inguinal area is higher, but pain is milder in patients who have undergone laparoscopic repair compared to open repair. The most representative indicator of the long-term success of the procedure is quality-analyzed life years, which is presumed higher in laparoscopic repair, demonstrating the superiority of the method. However, overall quality of life as determined through questionnaires was found to be similar in laparoscopic and open repair groups[23]. This result was also supported by data derived from studies focusing on the effectiveness of the techniques. Data from these two studies underline the comparable quality of life of patients from both repair groups. There were no statistically significant differences[24,25].

Besides quality-of-life markers, recurrence rates depict the success of the procedure in the years following surgery. Available data from prospective randomized studies have shown that only a few cases of recurrence following both laparoscopic and open repair were recorded. In addition, recurrence rates are similar between laparoscopic and open repair groups[20-23,25,26]. In five studies, more cases of recurrence were recorded in the laparoscopic group as an absolute number of cases, but the two groups did not differ significantly. A statistically significant difference ($P < 0.001$) in recurrence rates was only recorded in the retrospective study of Hynes *et al*[24], with a higher recurrence in the laparoscopic repair group. This was mostly attributed to operations performed by less experienced surgeons [24,26]. It must be noted that the study of Hynes *et al*[24] refers to operations performed in the early 2000s with the techniques and consumables available at that time. This may have been a contributing factor to the difference in recurrence in this study (Table 2).

IS LAPAROSCOPY WORTH THE COST?

A critical issue about laparoscopic repair is the cost in accordance with the postoperative quality of life. Two randomized prospective trials about cost-effectiveness of laparoscopic repair were found in the literature. Early data from a randomized controlled trial published in 2006 demonstrated that laparoscopic repair had a significantly higher cost and higher quality of life. The data supported the concept of open repair being more cost-effective for bilateral inguinal hernias[24]. In contrast, Ielpo *et al*[25] analyzed clinical outcomes, such as pain, recovery, recurrence and complications, costs, quality-adjusted life years and calculated cost-effectiveness. Their study showed a significantly higher cost of laparoscopic repair. At the same time, clinical outcomes of laparoscopic repair outperformed those of open repair. This demonstrates that laparoscopic repair may be cost-effective for bilateral inguinal hernias [25].

Laparoscopy has a priori higher cost, which is even higher when consumables are included. Although laparoscopic instruments may be reusable, making their use affordable, the main factor increasing the cost is the mesh fixation technique. Newer fixation techniques, such as self-gripping meshes and fibrin glue fixation have been proposed as more cost-effective fixation techniques[27]. It is of utmost importance to investigate cost-effectiveness. It must be noted that the latest randomized controlled trial analyzing cost-effectiveness indicated that laparoscopic repair in bilateral inguinal hernias is considered cost-effective. This difference between prior studies[24] and this one[25] likely derives from the fact that

Table 2 Recurrence rates

Ref.	Patients	Laparoscopic	Open
Sarli *et al*[20], 2001	43 (20 *vs* 23)	0%	4.34%
Mahon *et al*[21], 2003	120 (60 *vs* 60)	6.7%	1.7%
Ielpo *et al*[22], 2018	134 (61 *vs* 73)	6.6%	5.5%
Bignell *et al*[23], 2012	120 (60 *vs* 60)	7%	8%
Hynes *et al*[24], 2006[1]	1395 (687 *vs* 708)	8%	4%[a]
Neumayer *et al*[26], 2004	353 (175 *vs* 178)	4.57%	2.80%
Ielpo *et al*[25], 2018	165 (81 *vs* 84)	7.4%	4.8%

[1]Recurrence rates for both unilateral and bilateral hernias.
[a]$P < 0.01$.

with advances in laparoscopic surgery, necessary equipment along with consumables have become more accessible and more affordable. It should be emphasized that in the past few years more patients have undergone laparoscopic repair, so more patients have been enrolled in newer studies. This evidence is considered more representative[25].

IS THERE SUFFICIENT EVIDENCE?

All of the trials supporting the superiority of laparoscopic repair of bilateral hernias included only a small number of patients[20-27]. In the literature, there is only one large-scale retrospective non-randomized study. This particular study, which included more than 2800 patients with bilateral inguinal hernias, concluded that laparoscopic repair was at least non-inferior to the open repair and that it should be considered as "gold standard"[28]. As this study is retrospective, the level of evidence is not considered sufficient to set a "gold standard," but it still provides an indication. It is more than clear that more large-scale prospective randomized trials are needed to prove this point. The first studies regarding bilateral hernias were published in the late 1990s and early 2000s. Until recently, and for approximately 15 years, there were only a few studies published underlining the fact that there is research progress to be made to define laparoscopic repair of bilateral inguinal hernias as the "gold standard." The wide range of techniques used explains the diversity of the results of the existing trials. Uniformity of future studies is an issue that should be addressed. A consensus on the methods used between different study groups should be determined if significant results are to be extracted. In existing studies, study design depends mostly on each researcher and their clinical practice. Another issue is that some studies investigated laparoscopic repair in both unilateral and bilateral hernias. Newer studies have greater uniformity as they compare TAPP *vs* open repairs, but they lag behind in terms of patients enrolled[20-23].

WHICH TECHNIQUE SHOULD A SURGEON USE?

Laparoscopic techniques in hernia repair surgery have progressed over the past decades. Clinical outcomes of laparoscopic repair in bilateral hernias are very promising, as they outperform those of open repair in terms of pain in the immediate postoperative period and recovery. Over the years, these techniques have become more cost-effective. There is a shortage of evidence supporting the long-term superiority of these surgical procedures regarding quality of life as well as chronic groin pain. So far the results are controversial. To this day, it is still not possible to recommend a specific repair technique for bilateral hernias.

Available evidence is in favor of laparoscopic repair, but there is a lack of solid data. Future prospective studies are needed to compare the use of different techniques and surgical instruments as well as different meshes and fixation techniques. As existing evidence supports short-term superiority of the laparoscopic repair and suggests that it is a safe procedure when performed by a suitably trained surgeon, alongside the diminishing cost, it is promising to await future studies focusing on the long-term results of this method.

The answer to a surgeon's question "which technique should I use" is multifactorial. First, as there is still progress to be made in laparoscopy in order to establish it as the "gold standard" procedure, willingness of patients to undergo laparoscopic repair must be taken into consideration. It is crucial to

explain to them that a laparoscopic repair requires general anesthesia, whereas an open repair may be conducted in most cases under spinal anesthesia. In addition, we should not undermine the expertise of surgeons. As laparoscopic repair has a prolonged learning curve, it is more than clear that reforms in surgical training alongside special training programs are required to train surgeons, in order to familiarize them with these techniques. Only when these procedures are widely available and can be done safely, can we conclude that laparoscopic repair is the "gold standard" technique for the treatment of bilateral inguinal hernias.

CONCLUSION

Laparoscopic repair of bilateral inguinal hernias is associated with less postoperative pain and faster return to daily life compared to the open repair, but we do not have solid evidence supporting the long-term superiority of laparoscopic procedures over open repair regarding quality of life as well as chronic groin pain.

FOOTNOTES

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REVIEW

COVID-19 disease and autoimmune disorders: A mutual pathway

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Abstract

Coronavirus disease 2019 (COVID-19) is a real challenge for humanity with high morbidity and mortality. Despite being primarily a respiratory illness, COVID-19 can affect nearly every human body tissue, causing many diseases. After viral infection, the immune system can recognize the viral antigens presented by the immune cells. This immune response is usually controlled and terminated once the infection is aborted. Nevertheless, in some patients, the immune reaction becomes out of control with the development of autoimmune diseases. Several human tissue antigens showed a strong response with antibodies directed against many severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) proteins, such as SARS-CoV-2 S, N, and autoimmune target proteins. The immunogenic effects of SARS-CoV-2 are due to the sizeable viral RNA molecules with interrupted transcription increasing the pool of epitopes with increased chances of molecular mimicry and interaction with the host immune system, the overlap between some viral and human peptides, the viral induced-tissue damage, and the robust and complex binding between sACE-2 and SARS-CoV-2 S protein. Consequently, COVID-19 and its vaccine may trigger the development of many

autoimmune diseases in a predisposed patient. This review discusses the mutual relation between COVID-19 and autoimmune diseases, their interactive effects on each other, the role of the COVID-19 vaccine in triggering autoimmune diseases, the factors affecting the severity of COVID-19 in patients suffering from autoimmune diseases, and the different ways to minimize the risk of COVID-19 in patients with autoimmune diseases.

Key Words: COVID-19; SARS-CoV-2; Autoimmune Diseases; Vaccines

Core Tip: There is a mutual relation between coronavirus disease 2019 (COVID-19) and autoimmune diseases. Patients with immune deficiencies or autoimmune disorders are at a higher risk for infection with COVID-19, as they are frequently treated with anti-cytokine, glucocorticoids, and immunosuppressive drugs. Meanwhile, COVID-19 and its vaccine could trigger the development of autoimmune diseases. Therefore, a multi-purpose comprehensive social and family program with exercise and psychological support is highly needed for patients with autoimmune disorders to lessen the harmful effects of social isolation impeded during the COVID-19.

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INTRODUCTION

The coronavirus disease 2019 (COVID-19), with its global pandemic, which started with the first reported case in December 2019, is a real challenge for humanity. These challenges are due to the uncertainty about the origin of the virus, its rapid transmission, the difference in racial susceptibility, the wide variety of clinical presentations, the conflict in diagnosis, the rapid mutations that continuously elaborate, the disparity of the treatment regimens in the different parts of the world, and the high morbidity and mortality rates[1,2]. The virus that causes COVID-19, called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is a member of the beta coronaviruses group. This group is a part of a Coronaviridae family with spherical, positive-sense, non-segmented, single-stranded, and large (100–160 nm) RNA viruses[1].

SARS-CoV-2 is a single-stranded RNA virus with a positive sense and a unique pleomorphic or spherical, non-segmented envelope with distinctive crown-shaped peplomers or spikes[3]. It has four main structural proteins: spike protein (S), small envelope glycoprotein (E), membrane glycoprotein (M), and nucleocapsid protein (N). Other several accessory proteins are present and have particular functions. S protein is a sizeable trimeric glycoprotein that facilitates viral binding to host cells through binding to angiotensin-converting enzyme II receptors with its two non-covalently associated subunits. The first subunit (S1) binds to angiotensin-converting enzyme II (ACE2) with its subunit receptor-binding domain (RBD). The second subunit (S2 subunit) controls the fusogenic ability of the virus-cell membrane and fixes the S protein to the cell membrane[4]. The E protein is a small envelope glycoprotein of three variants, participates in viral assembly and virion release, and plays a critical role in the virus pathogenesis. M glycoprotein shapes the viral envelope and is accountable for transmembrane nutrient transporting and bud release. N protein is formed from the matrix protein and is present near the viral nucleic acid material within a capsid to help pack the viral RNA genome inside the viral envelope. This process is a fundamental component of the self-assembly and replication of the virus[5,6]. The virus's genome encodes for the four essential structural proteins (S, M, E, and N), hemagglutinin esterase, and another six accessory genes occupying the main part of the viral genome (about two-thirds). There are three well-defined variants of SARS-CoV-2: A, B, and C, according to their genomic differences[7].

PATHOGENESIS AND IMMUNOGENICITY OF SARS-COV-2

Despite being primarily a respiratory illness, COVID-19 can affect nearly every human body tissue, causing a broad range of illnesses. Similar to SARS-CoV, SARS-CoV-2 uses ACE2 receptors to enter the host cells. It uses the surface S glycoprotein with its two domains (S1 and S2) to bind at the RBD with

the ACE2 receptor and fuse the viral envelope membrane with the cell membrane. However, SARS-CoV-2 S proteins bind stronger with human ACE2 receptors than SARS[8]. These spike proteins have high antigenicity, as indicated by the elevated plasma anti-S neutralizing antibodies levels in convalescent patients[9].

The body localization and expression of ACE2 receptors could determine the potential target organs of SARS-CoV-2 infection and outline the disease progression and clinical consequences. ACE2 receptors were first reported in the heart, kidneys, and type-I and II alveolar cells. Then, recently high expression of ACE2 receptors was reported in the brain, eyes, nasal and oral mucosa, thyroid, esophageal epithelium, gastric mucosa, liver, cholangiocytes, pancreas, the smooth muscle cells, and enterocyte from the small intestine to the colon, skin, testis, ovary, uterus, vagina, and urinary bladder[10,11]. All these organs should be considered as a potential target for SARS-CoV-2 infection. ACE2 receptor expression may be absent in the bone marrow, lymph nodes, thymus, spleen, and numerous immune system cells[12]. The patients' differences in ACE2 receptor distribution and ACE2-SARS-CoV-2 mutual interactions could affect the disease pathophysiology, progression, and consequences. Many factors could affect ACE2 receptors distribution, including heritability, patient demographics, lifestyle, comorbidities, and drugs[13]. Meanwhile, soluble ACE-2 (sACE-2) is found in the serum or plasma due to shedding from the cell surface. These sACE-2 strongly interact with SARS-CoV-2 S protein and vasopressin to initiate receptor-mediated endocytosis, enabling SARS-CoV-2 to enter the host cells[14].

After viral entry into the body, it attaches to the mucosal cell, entering the cell either at the plasma membrane or the endosome through receptor-triggered endocytosis[15,16]. The receptor-dependent endocytosis starts by latching the RBD part of the S1 protein of the viral envelope to a pocket in the ACE2 receptor, fixing the virus to the cell membrane. Then, the transmembrane protease serine 2 present near ACE2 receptors cleaves a protein between the S1 and S2 units in a specific location, with the help of the Furin enzyme, which enables the viral entry into the cell after binding. The enzymatically induced cutting of S protein exposes previously hidden parts of the S protein, which undergo a series of remarkable conformational changes and more fixation into the cell membrane. Once inserted, S proteins pull back on themselves, pulling the membranes of the cell and the virus together to fuse. When the viral envelope starts to merge with the host cell membrane, it creates a fusion pore that allows the virus to release its genetic material into the cell cytoplasm of the infected cell[17,18].

After receptor engagement and viral replication inside the affected epithelial cells of the nasal cavity, there will be an initial asymptomatic phase for one to two days. During this phase, the virus continues to replicate and multiply without significant resistance by the innate cellular immunity. After this initial stage, the symptoms appear from 2-14 d. Once the SARS CoV-2 virus spreads to the lower respiratory tract, it stimulates a vigorous innate immune response with a more significant pro-inflammatory response that may progress to viral sepsis and other consequences of acute respiratory distress syndrome that may end with multisystem organ failures and even death[19].

Viral antigen presentation

After viral infection, T lymphocytes can recognize the viral antigens presented by major histocompatibility complex (MHC) class I on the surface of all the nucleated human cells and the platelets. This step is crucial for cytokine release and promotes CD8+ T cells cytotoxic activity. However, MHC class II can occasionally present the viral epitopes to CD4+ T cells[20,21]. The human leukocyte antigens (HLA) association is not very well-identified for SARS-CoV-2 infection, which could be crucial for preventing and treating COVID-19. However, a study by Tomita *et al*[22] showed that patients with HLA genotypes (HLA-A*11:01 or HLA-A*24:02) might efficiently produce T-cell-mediated immune responses to SARS-CoV-2 than patients with HLA-A*02:01. At the same time, reports documented the ability of SARS-CoV-2 to inhibit the expression of HLA-antigens. Giamarellos-Bourboulis *et al*[23] showed that the plasma-derived from patients with severe SARS-CoV-2 infection could inhibit the expression of HLA-DR on CD14+ monocytes, which could partially be reversed by Tocilizumab (IL-6 blocker), indicating the role of hyper-inflammation and the sustained cytokine production in inducing this immune dysregulation.

The innate immunity

The immune responses to SARS-CoV-2 start with the innate immune response by the interferon (IFN)-mediated pathways and the adaptive cellular and humeral immunity through the T lymphocyte and the antibody-mediated pathways. However, SARS CoV-2 can antagonize the IFN-mediated antiviral responses, allowing viral replication with a high early viral load and transmissibility[24]. The innate immune response to SARS-CoV-2 infection in the respiratory tract is mediated through alveolar macrophages and dendritic cells, inducing a cascade of inflammation to restrict virus replication effectively. This cascade of inflammation arises from the release of pro-inflammatory cytokines, particularly IL-18 and IL-1β, which explains the distinguished characteristic of neutrophilia and leukopenia commonly observed in patients with severe COVID-19[25]. The released inflammatory mediators recruit T lymphocytes and monocytes primarily, but not neutrophils, to the site of infection, which explains the lymphopenia and the raised neutrophil-lymphocyte ratio observed in most patients with COVID-19 [26]. However, this induced inflammatory cascade plays a significant role in the pathogenesis of severe organ injury and adverse disease outcomes[27]. The differences in patients' susceptibility to coronavirus

infection may be related to the differences in the Mannose-binding lectin (MBL) protein, which has a significant role in pattern-recognition molecules, one of the first-line host defense mechanisms against SARS-CoV-2 infections[28]. MBL pathway activates the complement pathway that promotes thrombosis and coagulopathy in severe COVID-19[29]. The viral RNA also activates Toll-Like Receptor 3, 7, 8, and 9, which accordingly activates the pathway including Nuclear Factor kappa B (NF-κB)[30].

This immune response is usually controlled and terminated once the infection is aborted. Nevertheless, in some patients, the immune reaction becomes out of control with excessive unwanted response ending with a cytokine storm with a low level of IFN in early-stage and high levels in late-stage, an excessive increase of interleukin (IL)-6, IL-2, IL-7, and IL-10, massive increase of granulocyte-macrophage colony-stimulating factor (GM-CSF), Macrophage Inflammatory Protein 1α (MIP-1α), Tumor Necrosis Factor-alpha (TNF-α), plasma-induced protein 10 (IP-10), monocyte chemotactic protein-1 (MCP-1), and Inflammatory Protein 1α (MIP-1α)[31-33]. This deviated immune response's exact mechanism is unknown but may be related to the antagonistic effects of viral N protein on the interferon signaling pathway. Interferons-mediated innate immunity is the first defense mechanism against viral infections, including COVID-19, through activating macrophages and natural killer (NK) cells, which destroy the virus-infected cells[26]. Interferon deficiency causes an elevation in pro-inflammatory cytokines, an inadequate antiviral response, ACE2 receptor upregulation, high viral load, and subsequent excessive inflammatory response[34,35]. Complement activity is essential in immunity modulation and can predict the clinical outcome of SARS-CoV-2 infection. Complement protein C3 activation occurs early in the course of COVID-19. It plays a significant role in enhancing prothrombotic and pro-inflammatory conditions with immune complex deposition in different organs that may proceed to extensive endothelial damage, acute respiratory distress syndrome, and even end-organ damage observed in severe cases of COVID-19[36,37]. Consumption of the complement proteins in the immune complexes explains the low levels of C3 and C4 observed in instances of severe COVID-19. Detection of low levels of C3 and C4 can be a warning sign of the need for additional management in patients admitted with COVID-19[38]. Immune complexes depositions induced-vascular injury and antibody-dependent enhancement increase viral replication in Fc-receptor expressing cells[39].

The adaptive immunity

The three main types of lymphocytes, B cells, T cells, and natural killer cells, play a vital role in clearing infections once they begin. Their plasma numbers correlate well with better survival. Lower leukocyte and lymphocyte numbers help the virus avoid the host immune response with a high viral load and transmission rate[40]. Once activated by SARS-CoV-2, natural killer T cells can prevent viral spread from the upper airways to the rest of the body and, consequently, determine the severity of the symptoms, the viral load, transmission to the community, and the disease outcome[41].

Although T and B lymphocytes do not express ACE2 receptors, some of them can still be infected by the SARS-CoV-2 virus, which indicates the presence of other receptors participating in the viral entry in some lymphocytes. After a few days from SARS-CoV-2 infection, naïve lymphocytes differentiate into Th2 and produce Th2 cell serum cytokines. The higher the levels of Th2 cell serum cytokines are, the worse the outcome is[42]. Some memory T cells can be primed by a previous animal or human coronavirus infections, so they can recognize some of the viral proteins, help clear SARS-CoV-2 and produce asymptomatic infections in many patients even in the absence of antibodies in their serum[43]. SARS-CoV-2 induces a direct cytotoxic effect on the lymphocytes to evade the immune system, resulting in lymphopenia, preventing cytokine storm, and diminishing the innate immune responses[44]. SARS-CoV-2 also upregulates many apoptosis-involved genes, including P53, which helps develop lymphopenia. This SARS-CoV-2-induced lymphopenia is prevalent in patients with old age or other comorbidities such as obesity, hypertension, or diabetes mellitus[45]. Lymphopenia could also result from increased leukocyte adhesion and extravasation due to SARS-CoV-2-induced endothelial dysfunction, particularly in old age and with comorbidities, augmenting the problem of lymphopenia [46]. Effector T cells are the leading players driving immune responses to achieve immune functions. These cells have both promoting and inhibitory regulatory functions of innate immunity. The maturation and differentiation of naïve-T cells to mature fully functioning effector cells are controlled by cytokines produced by activated cells of the innate and adaptive immune systems. SARS-CoV-2 induces enhanced inhibitory receptor expression on the surface of T cells due to cytokine activity or reduction of the regulatory T-cells. These inhibitory effects negatively exhaust the effector T cells and reduce the defense against SARS-CoV-2[47]. CD4+ T cells, CD8+ T cells, and B cells have a crucial protective role against SARS-CoV-2 infections. A decrease in CD4+ T cell number and function causes cytokine, neutralizing antibody production reduction, and reduced lymphocyte recruitment to lung tissue. These effects cause an increased risk of interstitial pneumonitis and delay the clearance of infection from the lungs. However, depletion of CD8+ T cells at the beginning of SARS-CoV-2 infection does not affect the viral clearance or replication[48].

B lymphocytes represent 15% of peripheral white blood cells and are responsible for the humoral immunity and protection against various pathogens through various immunologic functions, including antibody production. Specific immunoglobulin M (IgM) anti-SARS antibodies appear within two weeks after infection, reaching the peak in the third week, to gradually disappear until the end of the third month[49]. Immunoglobulin G (IgG) started to appear by the end of the second week, reaching the peak

by the end of the fourth week, and persisted for longer but not for a long time [in SARS-CoV-1, Ig G lasts for about two years][50]. Consequently, antibody levels can be used to determine the stage of SARS-CoV-2 infection. The levels of anti-SARS-CoV-2 antibodies decrease by about 50% within 1-3 mo following the beginning of the infection[51]. However, some cases with agammaglobulinemia infected COVID-19 showed full recovery without functioning B-cells[52,53]. The antibody response may help inhibit viral replication through neutralization and blocking the viral entry, egress, or fusion with the host. However, enhancing antibodies may counteract the neutralizing antibodies. Antibodies can enhance viral infections and participate in COVID-19 pathogenesis *via* antibody-dependent enhancement. The level of enhancing antibodies is positively correlated with pro-inflammatory mediators levels and negatively correlated with anti-inflammatory mediators. Which has the upper hand, the neutralizing or enhancing antibodies depend on the dominant antibody type concentrations and affinity[54,55]. Abnormal B lymphocytes maturation and conversion to macrophage-like cells caused by the viral S protein impairs the immune system's humoral and cellular elements in responding to severe infection with SARS-CoV-2[56]. Table 1 shows the various factors that affect the severity of infection with COVID-19.

AUTOIMMUNITY AND CROSS REACTIVITY OF SARS-COV-2

In antigenic or molecular mimicry, common antigenic sites are shared between microorganisms and the host tissue. The microorganism-triggered immune response is directed against the microorganism and the host cells with the common antigenic determinant. This deviated autoimmune response is responsible for developing many autoimmune disorders in humans. Recently, it has been observed that several human tissue antigens showed a strong reaction with antibodies directed against SARS-Cov-2. This antigenic mimicry was observed for many SARS-CoV-2 proteins, including but not limited to SARS-CoV-2 S, N, and autoimmune target proteins[57]. These induced antibodies can react with a wide variety of human tissues and proteins such as skin, respiratory, digestive, cardiac, and nervous tissues, producing a wide array of autoimmune disorders with extensive cellular, tissue, and organ damage observed in severe COVID-19 cases[58]. The cross-reactivity of SARS-CoV-2 is not limited to the human body. SARS-CoV-2 also has cross-reactivity with SARS-CoV, as patients with COVID-19 can produce IgG and IgM antibodies able to react with SARS-CoV. This observation is fundamental as it helps understand that some patients may have mild or aggressive COVID-19. Previous infection with SARS-CoV with pre-exciting antibodies that can cross-react with SARS-CoV-2 may explain this variation in the clinical presentation in patients with COVID-19. However, recovery from SARS-CoV infection might not protect against SARS-CoV-2 and vice versa[59]. Cross-reactivity between SARS-CoV-2 and other human coronaviruses, especially beta coronaviruses (particularly SARS-CoV and MERS-CoV), may explain numerous phenomena. The increased pathogenicity and severity of SARS-CoV-2 infection in areas with common pre-existing SARS-CoV infection is due to the possible presence of enhancing cross-reactive antibodies against those common coronaviruses[60]. Enhancing cross-reactive antibodies to SARS-CoV-2 in patients previously exposed to SARS-CoV can explain the early response with higher titers in older age and the milder symptoms in the pediatric age[61,62]. However, the lower prevalence of COVID-19 in the pediatric age is multifactorial and could be related to the age-dependent immaturity of ACE2 receptors in children[63]. The tissue damage induced by the cross-reactive autoantibody induces the release of more self-antigens, activating more autoreactive T-cells, producing more self epitopes, and sparking autoimmunity[64]. Cross-reactive antibodies also raise a question about using convalescent plasma to treat patients with SARS-CoV-2 infection to neutralize SARS-CoV-2. However, convalescent plasma may lack effectiveness and, on the other hand, may induce endothelial damage due to the transmission of cross-reactive enhancing antibodies[65]. Cross-reactivity is also of paramount importance in the vaccination industry, considering SARS-CoV-2 cross-enhancing or neutralizing epitopes to minimize the vaccine side effects and vaccine-induced autoimmunity[66].

SARS-COV-2 INDUCED AUTOIMMUNE AND AUTO-INFLAMMATORY CONDITIONS

A variety of factors may trigger autoimmunity by generating a hyperstimulated immune system. The terms exposome, infectomes, and autoinfectomes are recently introduced in autoimmunity. Exposome describes all the environmental triggers (exogenous or endogenous) that the host could expose to it. Infectomes are all infectious microbes that the host can be exposed to during his/her life. In the same way, autoinfectomes are all infectious agents that can trigger autoimmunity upon exposure[67]. The ability of SARS-CoV-2 to initiate autoimmune and autoinflammatory responses is related to many factors. The SARS-CoV-2 can induce a state of the hyperstimulated immune system with changes in the circulating leukocyte and an extensive increase in the levels of the pro-inflammatory cytokines, known as "cytokine release syndrome" in patients with variable degrees of COVID-19[32]. The large RNA with 30,000 nucleotides and the complex transcriptome with the interrupted transcription and recombination activities increase the chance of interaction with the host immune system[68]. The interrupted RNA

Table 1 Factors affecting the severity of coronavirus disease 2019 infections

Factor		Example
Viral-related factors		The viral load[24]; Mutation/virulence; Previous infections with other Coronaviruses *e.g.*, SARS-CoV[43,59]
Host-related factors:	**Demographic factors**	Patients' age[61,62]
		Gender[80,182]
		Race/ethnic group
	Physiological	Pregnancy[215]; Personel differences in ACE2 receptors distribution[13]
	Pathological factors	Presence of comorbidities such as obesity, hypertension, tuberculosis, HIV, anemia, nutritional deficiencies, or diabetes mellitus[13,45,159,169,171,181]
	Immunological factors	The type of HLA-antigen[20-23]
		The plasma numbers of B cells, T cells, and natural killer lymphocytes[40,41]
		The hemoglobin and ferritin levels[216]
		The levels of C3 and C4[38]
		The differences in the MBL protein[28]
	Environmental factors	Socioeconomic status[217]
		Overcrowding[218]
		Smocking[205]
		Alcohol consumption[204]
		Particular occupations: Occupations that involve a higher degree of physical proximity to others over long periods [219]
	Pharmacological factors	Certain drugs increase the severity (*e.g.*, rituximab, high-dose corticosteroid)[140,187,191]. Certain drugs decrease the severity (*e.g.*, ubiquinone, ezetimibe, flecainide, rosuvastatin, artificial tears, licorice)[214]
		Vaccination status of the patients

ACE2: Angiotensin-converting enzyme II; HLA: Human leukocyte antigens; HIV: Human immunodeficiency virus; MBL: Mannose-binding lectin; SARS-CoV: Severe acute respiratory syndrome coronavirus 2.

transcription and recombination produce a wide variability of protein sequences with a powerful resource of epitopes with molecular mimicry, another reason for stimulating the immune system and inducing autoimmunity associated with COVID-19[69]. There is an overlap between some viral and human peptides, so that if altered or mutated could initiate autoimmunity. From these human peptides; cerebellum-2 (which protects against multiple sclerosis), follistatin-related protein 1 (which has anti-hypoxia-induced pulmonary hypertension), Solute carrier family 12 member 6 (responsible for electroneutral potassium-chloride cotransport), and olfactory receptor 7D4 (responsible for the sense of smell)[70]. Tissue damage may result from the viral infection causing cell death and the release of self-proteins to be identified by the host immune system as foreign material and spark the process of autoimmunity[71]. At the same time, there is a hypothesis that sACE-2, which usually binds strongly with SARS-CoV-2 S protein, forms a complex, stimulating the production of anti-ACE2 antibodies and triggering type II and III hypersensitivity reactions and Type IV cellular immune reactions against the viral particles attached to sACE-2, and autoimmunity cascade. The virus-activated T cells could injure the self-tissues by initiating an inflammatory milieu or directly damaging the cells[72]. Table 2 summarizes the causes of the increased immunogenic effect of SARS-CoV-2.

Infection with SARS-CoV-2 can serve as infectome induce a range of autoimmune and auto-inflammatory conditions such as Multisystem Inflammatory Syndrome in Adults (MIS-A), Multisystem Inflammatory Syndrome in Children (MIS-C), and various autoimmune/rheumatic manifestations with a proposed link between the autoimmune and autoinflammatory sequelae of SARS-CoV-2 infection[73]. MIS-C may include Kawasaki-like disease, toxic shock syndrome, Kawasaki disease (KD) shock syndrome, macrophage activation syndrome, and myocarditis. MIS-A, contrary to MIS-C, is not well defined with a hyperinflammatory state and inconsistent features of KD[74]. Although children usually encounter a milder COVID-19 than adults, the severe MIS-C that followed the disease in some children brought several unanswered questions to the scientific community[75].

Patients with COVID-19 may develop a wide variety of autoimmune disorders such as arthritis, antiphospholipid antibody syndrome (APS), MIS-A/C, Kawasaki and Kawasaki-like disease, antiphospholipid syndrome, systemic vasculitis, systemic lupus erythematosus (SLE), hemophagocytic lymphohistiocytosis, autoimmune blood disorders (such as idiopathic thrombocytopenic purpura, autoimmune

Table 2 Factors that increase the rate of autoimmunity in coronavirus disease 2019

The ability of the virus to infect nearly all the human body tissues
Large RNA with interrupted transcription increases the pool of epitopes with increased chances of molecular mimicry and interaction with the host immune system
The overlap between some viral and human peptides
The viral-induced tissue damage increases the chance of deviated immune system
The immunogenic effect of the robust and complex binding between sACE-2 and SARS-CoV-2 S protein

SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2.

thrombotic thrombocytopenic purpura, and autoimmune hemolytic anemia), neurological autoimmune disorders (such as encephalitis, cranial neuropathies, Guliian Barre syndrome, myelitis, and optic neuritis, acute disseminated encephalomyelitis {ADEM}, and multiple sclerosis), interstitial lung disease, autoimmune ocular disorders (Retinal vein vasculitic occlusion), renal disorders (Crescentic glomerulonephritis, Goodpasture syndrome), inflammatory bowel disease, and autoimmune endocrine disorders (such as diabetes mellitus and subacute thyroiditis)[76].

Risk factors increasing the likelihood of autoimmune diseases in patients with COVID-19

Infections with SARS-CoV-2 increase the likelihood of autoimmune disease development as about 50% of the patients have autoantibodies in their blood, even with mild disease, and the risk increases with increasing severity. Severe disease is usually associated with a higher viral load with robust immune stimulation and higher antibody levels. There is a strong association between immune hyperactivation and excessive cytokine release in patients with severe COVID-19. However, mild COVID-19 or even asymptomatic infection may also trigger autoimmune disorders[77]. Demographic features such as female gender, old age, overweight, or obesity generally increase the risk of developing autoimmune diseases, particularly with COVID-19. Aging causes functional impairment of the immune with potentially higher autoreactive antibody levels[78]. Although females usually have milder diseases than males with higher recovery rates, they have more chance of autoimmune disorders. The risk difference of autoimmune disorders between males and females is related to sex hormone differences as androgens like testosterone are immunosuppressive, while estrogen may enhance or reduce immune response[79]. Particular ethnic populations are more genetically predisposed to have autoimmune disorders following SARS-CoV-2 infection, such as Caribbean descent, sub-Saharan, Asian, Black, and mixed ethnicity[80]. Nucleic acid vaccine administration may increase the risk of autoinflammatory and autoimmune disorders, especially in young females. In addition, a pre-existing autoimmune disorder is a risk factor for another autoimmune disorder or more severe symptoms following COVID-19[81]. Gut dysbiosis is a risk factor for both COVID-19 and autoimmune diseases. Ivermectin, a commonly used drug in managing COVID-19 in certain countries, induces significant alteration of gut microbiota, which may increase the risk of autoimmune disorders. However, more studies are needed to confirm this hypothesis[63,82].

Common autoantibodies with SARS-CoV-2 infection

Patients with COVID-19 may develop multiple categories of autoantibodies and autoimmune diseases. However, the clinical significance of these antibodies needs more elaboration. From these antibodies are anti-nuclear antibodies (ANA), antiphospholipid antibodies (as lupus anticoagulant, Anti-β2 glycoprotein 1, and anticardiolipin), anti-Interferon-gamma (Anti-IFN-ɣ) antibodies, anti-melanoma differentiation-associated gene 5 (Anti-MDA5) antibodies, and anti-ACE2 autoantibodies[83]. ANA antibodies are found in 4-50% of patients with COVID-19, especially with old age, even without autoimmune disease. Presence of ANA antibodies in patients with COVID-19 increases the incidence of neurologic and thrombotic complications and unfavorable outcomes[76]. Anti-type-I interferon (IFN) antibodies are present in 10.2% of patients presented with severe COVID-19 pneumonia[84]. Antiphospholipid antibodies (anticardiolipin and/or anti-β2 glycoprotein 1) are present in a significant portion of critically ill patients with COVID-19. These antibodies and elevated factor VIII may contribute to hypercoagulopathy in severe cases of COVID-19[85]. Anti-MDA5 antibodies are associated with the rare disease amyopathic dermatomyositis. They are also present in more than 40% of patients with severe COCID-19. Higher titers of Anti-MDA5 antibodies are associated with more severe disease and a higher risk of death[86]. Anti-ACE2 antibodies are present in many patients with COVID-19 and are associated with low plasma levels of sACE-2 and increasing angiotensin II levels, which triggers a pro-inflammatory state that causes symptoms of post-SARS-CoV-2 Acute Sequelae[87]. The SARS-CoV-2 virus causes damage to the human brain *via* complex indirect processes and stimulates autoantibody formation, predominantly against brain-based antigens (autoantibodies against contactin-associated protein 2, ganglioside GD1b, and myelin oligodendrocyte glycoprotein), inducing a wide variety of

COVID-19-triggered neurological complications[64].

COVID-19-INDUCED AUTOIMMUNE DISEASES

Multisystem inflammatory syndromes (MIS-A, MIS-C, and MIS-A/C)

Multisystem inflammatory syndrome (MIS) is a rare acute and non-chronic but seriously complicates COVID-19 in adults and children. It is currently a distinct phenomenon of severe COVID-19 due to the frequent absence of respiratory involvement. The MIS pathogenesis is unclear but primarily due to the autoimmune process. MIS-A associated with COVID-19 infection usually occurs in adults aged 35-54. Clinical recognition of MIS-A is confused with other hyperinflammatory manifestations of COVID-19, which makes MIS-A challenging to distinguish from acute biphasic COVID-19 and post-acute sequelae of SARS-CoV-2 infection[88]. To its name, MIS-A involves multiple organs and systems with at least one or more extrapulmonary organs (an average of 4-5 organs). The most affected organs are hematologic, cardiovascular (myocarditis, pericardial effusion, hypotension, cardiac dysfunction, heart failure, arterial or venous thrombosis, and cardiogenic shock), gastrointestinal tract (diarrhea), acute liver injury, respiratory system (dyspnea), skin manifestations (polymorphic rashes and other mucocutaneous manifestations), renal, and nervous system (severe mononeuritis multiplex[89-91].

It can be diagnosed according to the CDC criteria for defining MIS-A. It should occur in adults aged 21 years or older, with manifestations that need hospitalization for more than 24 h, as determined by clinical and laboratory criteria. Clinical criteria include fever (≥ 38.0 °C) for ≥ 24 h before hospitalization or within the first three hospitalization days plus three or more of the following clinical criteria; one of them at least should be from the primary criteria. Primary clinical criteria include severe cardiac involvement, skin rash, and non-purulent conjunctivitis. Secondary clinical criteria include; new-onset neurologic manifestations, non-medication-related hypotension or shock, abdominal manifestations (abdominal pain, vomiting, or diarrhea), and thrombocytopenia. Laboratory criteria include evidence of recent SARS-CoV-2 infection (positive PCR, antigen, or antibody) and elevated at least two inflammatory markers from the following: erythrocyte sedimentation rate, C-reactive protein, IL-6, ferritin, and procalcitonin[92]. MIS-A should be differentiated from meningitis, intra-abdominal sepsis, KD, drug reaction, and haemophagocytic lymphohistiocytosis. It is treated with corticosteroids, anticoagulants (*e.g.*, heparin, enoxaparin, aspirin), immune modulators such as Infliximab (TNF inhibitors), Tocilizumab (IL-6 receptor inhibitor), Anakinra (IL-1 receptor antagonist), and intravenous immunoglobulin (IVIG). Patients who develop shock/hypotension require intensive care unit admission, vasoactive medications, and respiratory support with mechanical ventilation[93].

MIS-C occurs in people younger than 21, a few weeks after infection with SARS-CoV-2. The affected children have a fever with clinical evidence of severe disease requires hospitalization and multisystem (more than two) organ involvement (heart, kidneys, respiratory, gastrointestinal, hematologic, skin, and/or nervous system) without other possible reasons explaining the manifestations, evidence of recent infection with SARS-CoV-2 (positive PCR, antigen or antibody), and presence of markers of systemic inflammation (high ferritin, fibrinogen, procalcitonin, lactic acid dehydrogenase, C-reactive protein, erythrocyte sedimentation rate, D-dimer, lactic acid dehydrogenase, or interleukin 6, reduced lymphocytes, elevated neutrophils, and low albumin)[94,95]. As MIS-C frequently affects the heart, we may need to perform B-type natriuretic peptide, cardiac enzymes and Troponin I or T, electrocardiogram, and echocardiography. According to the organs affected, other laboratory tests may be needed [96]. MIS-C is primarily treated with supportive care, fluid resuscitation, and inotropic support as a cardiogenic shock is one of the most severe presentations. Respiratory support is indicated with impending respiratory failure. Extracorporeal membranous oxygenation is rarely required. IVIG, steroids, other anti-inflammatories, and anticoagulants are frequently used. Antibiotics may be used with suspected sepsis. Aspirin is commonly prescribed due to the frequent involvement of coronary arteries[97,98].

KD-COVID-19

COVID-19 is usually milder, less frequent, and has less mortality in children than adults due to less maturity and function of ACE2 receptors. Since the early beginning of 2020, there has been an increased reporting of children presented with fever, signs, and features of systemic inflammation common with KD[99]. KD is an acute, usually self-limited systemic inflammatory disease of medium- and small-sized vessels. It mainly involves children under five years of age with higher frequency in children from Asian countries like Japan, where it was first described in 1967[100]. It is usually preceded by upper respiratory tract infections, particularly with RNA viral infection of the upper respiratory tract, as viruses were usually isolated from the mucous obtained from the bronchial epithelium[101]. Despite being a self-limited disease, hemodynamic instability and shock may occur in some cases, known as KD shock syndrome. About 20%–25% of untreated patients of KD develop changes in the coronary arteries, ranging from asymptomatic dilatation or aneurysms to massive aneurysmal dilatation of the coronary artery with thrombosis and myocardial infarction that could progress to sudden death[102].

Symptoms of COVID-19-associated MIS-C may have the standard features of KD. Therefore, it is essential to differentiate between classical KD and COVID-19 (KD-COVID-19). The table shows the differences between the classic KD and KD-COVID-19 [also known as pediatric inflammatory, multisystem syndrome temporally associated with SARS-CoV-2 infection' (PIMS-TS) in Europe and 'multisystem inflammatory syndrome in children (MIS-C)] in the United States. KD-COVID-19 usually occurs in older children, higher incidence of myocarditis and cardiac involvement, more gastrointestinal and meningeal manifestations, shock, hemodynamic failure, manifestations of macrophage activation syndrome, frequent leukopenia, significant lymphopenia, thrombocytopenia, high ferritin, procalcitonin, cardiac enzymes, and troponins than classic KD[103]. Recent or current evidence of SARS-CoV-2 infection is needed to diagnose KD-COVID-19. Patients with KD-COVID-19 have more severe diseases than those with classic KD and frequently need hospitalization and intensive care support[104]. Early diagnosis of COVID-19, recognition of KD-COVID-19, and rapid therapy initiation are vital for effective management, recovery, and prevention of end-organ damage and mortality[105]. IVIG therapy is usually effective in KD-COVID-19, but the resistance rate is more common than in children with classic KD, and steroid therapy is generally needed. In refractory cases to IVIG, pulse intravenous methylprednisolone therapy and aspirin are used, especially when a suspected cardiac injury is present[106]. Hydrogen gas inhalation treats KD-COVID-19 as a stable and efficient antioxidant that positively affects oxidative damage, improves inflammation and cell apoptosis, and antagonizes abnormal blood vessel inflammation[107]. Table 3 summarises the differences between the classic Kawasaki Disease and Kawasaki Disease -COVID-19.

APS

There is a high prevalence of venous thrombosis and embolism in patients with COVID-19, especially in severe cases (about 25% to 31% of those without thromboprophylaxis). Consequently, researchers investigated the possible underlying predisposing factors such as hypoxia, immobilization, or disseminated coagulopathy[108]. Serum antiphospholipid antibodies (aPLs), the whole mark of APS, are found in 1%-5% of the healthy population, and their titer increases with age. These rates are comparable to patients with COVID-19 (from 2.7% to 13.4%), which decreases the possibility of recognizable association with thrombosis[109,110]. Another study showed that serum antiphospholipid antibodies might be found transiently in up to 12% of young, healthy subjects, increased to 18% in older adults with chronic diseases[111]. The presence of aPL is not enough to develop APS; a second hit such as aging, critical illnesses, or infections is needed to trigger the development of APS. APS is characterized by documented thrombotic and/or pregnancy-related morbidity in the presence of persistent medium to a high titer of aPLs. To diagnose APS according to Sydney criteria, we need to have persistent high titers of lupus anticoagulant, anticardiolipin antibodies IgG or IgM, or anti-β2glycoprotein-1 IgG and/or IgM for at least 12 wk[112]. However, these criteria need to be modified to limit testing to lupus anticoagulant and anti-β2glycoprotein-1 IgG and to omit anticardiolipin antibodies and anti-β2glycoprotein-1 IgM from laboratory testing. Lupus anticoagulants and anti-β2glycoprotein-1 IgG are associated with a higher risk of thrombosis, particularly lupus anticoagulants[113].

Some studies elucidated high levels of lupus anticoagulants in patients with COVID-19. However, it is unknown whether lupus anticoagulant was newly produced with COVID-19 or increased in a previously present titer[114]. Another study by Xiao *et al*[115] showed that aPLs were present in 47% of critically ill patients due to COVID-19. They also analyzed the risk of developing cerebral infarction by the type of aPLs, with IgA anti-β2glycoprotein-1 being the aPL antibody associated with the highest infarction risk, followed by IgA anticardiolipin antibodies and IgG anti-β2glycoprotein-1. The study also showed that these antibodies need to appear five to six weeks after the disease onset, indicating that a long disease course increases the risk of developing APS and, consequently, thrombotic complications. A severe fatal form of APS (Catastrophic APS) was recorded in some patients with COVID-19. However, there is no current strong evidence of CAPS association with COVID-19. CAPS presented with acute multiorgan involvement (three or more organs, systems, and/or tissues), proof of widespread vascular occlusions, intense hypercoagulable state, and elevated titers of aPLs. Lupus anticoagulant, anticardiolipin IgG, and anticardiolipin IgM were seen in 83%, 81%, and 49% of patients with CAPS [116]. Some factors usually trigger CAPS, such as viral infections, including COVID-19, especially pulmonary infections. SARS-CoV-2 may aggravate the pathogenic effects of APS, initiating inflammatory and prothrombotic cascades. The positive tropism of SARS-CoV-2 towards the vascular endothelium may also alter the COVID-19 clinical presentation in susceptible patients and initiate flaring up of underlying vascular diseases. As CAPS has a high mortality rate, approaching 50%, timely identification and management are vital[117]. It responds to plasmapheresis or plasma exchange. However, it poorly responds to anticoagulant therapy with high mortality risk[118].

SLE

SLE is a chronic multisystem autoimmune disease with varied relapsing or remitting clinical manifestations. It is more common in females and certain ethnic groups, such as African Americans and Hispanics. Due to the aberrant immune system activity in SLE, immune complexes and autoimmune antibodies are significantly produced against cytoplasmic and nuclear antigens[119]. Few patients reports documented newly diagnosed SLE in patients with COVID-19. There is a wide variation in the

Table 3 Differences between the classic Kawasaki disease and Kawasaki disease - coronavirus disease 2019

	Classic KD	KD-COVID-19
Age	Children < 5 yr of age	Older age
General condition	Less ill than in KD-COVID-19	More severely ill
Gastrointestinal & meningeal signs	Less common	More common
CBC	Leucocytosis, anemia, & thrombocytosis. Thrombocytopenia may occur	Leukopenia with marked lymphopenia, thrombocytopenia
Ferritin	Increased	Markedly increased
Incidence of myocarditis	Subclinical myocarditis is nearly present in all patients. However, clinically evident myocarditis is uncommon.	Very high, up to 60.4% in patients with KD-like multisystemic disease.
Response to IV gamma globulins	Well-responding	Resistance to IVIG therapy is common.
Adjunct steroids	May be needed	Usually needed

COVID-19: Coronavirus disease 2019; CBC: blood cell count; KD: Kawasaki disease; IVIG: Intravenous immunoglobulin.

clinical presentation in the reported cases. It presented with manifestations of serositis (pericardial and pleural effusion), renal manifestations (nephritis, proteinuria), skin manifestations (varicella-like rash), cardiac dysfunctions (pericardial tamponade, ventricular dysfunction), secondary APS, neurological complications (neuropsychiatric symptoms, cerebral hemorrhage), hematological disorders (anemia, positive direct Coombs, hemolytic anemia, lymphopenia, thrombocytopenia,), finger vasculitis, low complement, and presence of autoantibodies (aPL, ANA, and anti- dsDNA). Patients with COVID-19-associated SLE had a high mortality rate reaching 50%. Hence appropriate and prompt diagnosis and management are highly indicated to decrease morbidity and mortality. Renal involvement carries the worst prognostic predictor with the highest mortality rate. The treatment should be individualized and may involve glucocorticoids, plasma exchange, hydroxychloroquine, anticoagulation, tocilizumab, and intravenous immunoglobulins[120-123].

Autoimmune-like neurologic disease

SARS-CoV-2-triggered inflammatory and autoimmune cascades may affect the nervous system, producing various neurological complications. About 60% of patients with COVID-19 suffer from anosmia (loss of smelling) and ageusia (loss of taste sensation), which verifies the hypothesis of its neurovirulence[48]. This high percentage of anosmia and ageusia observed with SARS-CoV-2 infection indicates the high viral neurotropism with the olfactory nerve serves as a portal of brain entry. However, anosmia and ageusia can be the first or only symptoms present in some patients with COVID-19[124]. Another portal of brain entry is through retrograde axonal transport *via* peripheral and cranial nerves. An example of this portal of entry is SARS-CoV-2-associated Guillain-Barre syndrome, an acute inflammatory, demyelinating, sensorimotor polyradiculoneuropathies frequently reported in patients with COVID-19. It results from the autoantibodies production that cross-react with myelin components gangliosides and glycolipids present in the peripheral nerves due to molecular mimicry. These autoantibodies cause peripheral nerve demyelination and axonal damage in a progressive ascending pattern[125]. It occurs primarily secondary to SARS-CoV-2-induced immune reaction, as the virus was not detected in the cerebrospinal fluid of any patient suffering from GBS[126].

Miller Fisher syndrome (MFS) and polyneuritis cranialis were rarely reported as autoimmune neurological complications of SARS-CoV-2 infection. They are other examples of the virus's neurotropism and its ability to rapidly spread to the different brain areas, including the thalamus and the brain stem. MFS is classically present with acute onset of a triad composed of external ophthalmoplegia, loss of tendon reflexes, and ataxia[127]. Polyneuritis cranialis is a rare, gradual, and slowly progressive disorder involving multiple cranial nerves (usually IV, V, VI, and VII). Viral infection often preceded these disorders, which triggered an immune-mediated mechanism. Few reported cases followed SARS-CoV-2 infection. CSF showed albuminocytological dissociation, and the patients had a significant elevation of inflammatory mediators, such as the interleukin-8. It can be successfully treated with IVIG[128]. Other reported neurological disorders related to COVID-19 aberrant immune response include acute motor-sensory axonal neuropathy, acute transverse myelitis, acute necrotizing encephalopathy, acute necrotizing myelitis, and acute disseminated encephalomyelitis[129].

Post-COVID-19 pneumonia lung fibrosis

Progressive pulmonary fibrosis following COVID-19 pneumonia is one of the severe complications of SARS-CoV-2 infections that could be associated with irreversible lung dysfunction. Post-COVID-19

pulmonary fibrosis is multifactorial, with many theories explaining the potential causes of post-COVID pulmonary fibrosis. One theory is the cytokine storm caused by an aberrant immune mechanism that triggers pulmonary fibrosis[130]. IL-6 is a pro-inflammatory cytokine with a pro-fibrotic activity that activates the neutrophils and their accumulation at the injury site. Neutrophil accumulation causes proteases and oxygen-free radical release causing pulmonary interstitial edema and acute inflammation [131]. Annexin A2 is crucial to protect against pulmonary fibrosis as it is essential to activate endogenous tissue plasminogen activator to lyse clots and promote fibrin clearance and pulmonary fibrinolysis[132]. Anti-Annexin A2 antibodies are associated with systemic thrombosis, cell death, and non-cardiogenic pulmonary edema. Annexin A2 inhibition can induce diffuse alveolar damage and pulmonary fibrosis in patients with severe COVID-19[133].

Arthritis

Arthritis was reported early in COVID-19 or lately after the resolution of the disease. Different types of arthritis were reported in patients with COVID-19; viral arthritis, reactive arthritis, chronic arthritis, and rheumatoid arthritis[134]. López-González *et al*[135] reported joint pain in some patients with COVID-19; some did not have other signs of arthritis. They also reported crystal-induced arthritis (gouty with monosodium urate and pseudogouty with calcium pyrophosphate) in some patients. Ono *et al*[136] reported the occurrence of reactive arthritis three weeks later in a patient who developed severe COVID-19 pneumonia. The patient improved with anti-Inflammatory non-steroidal drugs and intra-articular corticosteroid injection. Reactive arthritis generally develops one to three weeks after the infection. The precise mechanisms of COVID-19-induced arthritis are not entirely identified. It could be related to viral-induced macrophage activation with subsequent release of cytokines and chemokines in high amounts, sparking the inflammatory process[82]. Although viremia is expected in reactive arthritis, SARS-CoV-2 was detected only in the blood in 15% of cases with COVID-19. Consequently, molecular mimicry may explain arthritis pathogenesis[137]. Inflammatory mediators such as Interleukin 17 A are present in patients with reactive arthritis, spondyloarthritis, and COVID-19 -induced hyperinflammatory state[138].

COVID-19-induced vasculitis

SARS-COV-2 can directly infect the vascular endothelium causing endotheliopathy. Indirect damage to the vascular endothelium can also be induced by the inflammatory mediators triggered by COVID-19 [139]. Few case reports are documenting the development of COVID-19-associated vasculitis with positive anti-neutrophil cytoplasmic antibodies (ANCA). Uppal *et al*[140] described two cases of pauci-immune glomerulonephritis with high perinuclear-ANCA titer during SARS-CoV-2 infection. They clinically improved with the treatment of COVID-19 and the use of rituximab. Hussein *et al*[141] described a female patient who developed granulomatosis with polyangiitis and alveolar hemorrhage during COVID-19 infection. She was treated successfully with pulse steroid therapy, plasmapheresis, and IVIG. These reported cases clarify the importance of vascular endothelium in the pathophysiology and clinical course of COVID-19 and the need for a better understanding of the endothelial biology in patients with COVID-19[142].

Skin autoimmune disorders

Cutaneous manifestations of COVID-19 are common and may involve erythematous, maculopapular, urticarial petechial skin rashes, or diffuse disseminated erythema. The rashes may appear with the onset of the disease and may not correlate with the disease severity[143]. Pityriasis rosea-like rashes were reported in one patient with mild COVID-19[144]. Various reports described acral chilblain lesions due to vacuolar interface dermatitis with superficial and deep perivascular and periadnexal lymphohistiocytic infiltration[145,146]. Violaceous papules and digital swelling occur due to diffuse perivascular dense lymphoid infiltration of the dermis and hypodermis[147]. Desquamation of the peripheral digits may occur in younger children with severe disease or as a sign of KD-COVID-19[148]. Daneshgaran *et al* [149] showed that underlying mechanisms of skin involvement in patients with COVID-19 are related to cytokine release syndrome, coagulation and complement systems activation, or direct virus-induced skin damage with endothelial damage of the dermal vasculatures.

POST-VACCINATION AUTOIMMUNE DISORDERS

The vaccines work by provoking an immune response against specific antigens in the target organism that causes the disease with a long-lasting memory T-cell response. Vaccine adjuvants are used to enhance the immune response against the vaccine. However, these adjuvants can trigger autoimmune responses[150]. Vaccines have been involved in triggering autoimmune diseases for a long time. GBS was reported with Flu and Human Papilloma vaccines, and idiopathic thrombocytopenia occurred in some patients receiving the Measles-Mumps-Rubella vaccine[151]. COVID-19 vaccines can trigger a wide range of skin reactions; from non-specific local injection-site reactions to Type-I hypersensitivity reactions (*e.g.*, urticarial rashes, angioneurotic edema, and even anaphylaxis) to Type-IV delayed

hypersensitivity reactions (including delayed large skin lesions ("COVID arm") at the injection site, inflammatory reactions in a previous skin lesion, and more frequently erythema multiforme-like and morbilliform rashes[152]. COVID-19 vaccination-induced autoimmune skin disorders include immune thrombocytopenia, leukocytoclastic vasculitis, and lupus erythematosus[153].

Severe anaphylaxis was reported with Pfizer-BioNTech and Moderna vaccines. Consequently, the CDC recommends that prefilled epinephrine syringes be available in vaccination centers and observe the vaccinees for 15 or 30 min[154]. Delayed-type or T-cell mediated hypersensitivity adverse reactions were reported in 0.8% of the vaccinees near the injection site[155]. SARS-CoV-2 vaccination may also be complicated by autoimmune diseases that involve the skin, such as lupus erythematosus (LE), bullous pemphigoid, vitiligo, alopecia areata, and leukocytoclastic vasculitis[156,157]. Akinosoglou *et al*[159] reported bilateral elbow itchy annular granulomatous rash due to cutaneous small cell vasculitis after the first dose of the Pfizer-BioNTech vaccine. The rashes spontaneously resolved without medications within three to four days[158]. These vaccine-related adverse effects could be related to a pre-existing dysregulated immune status that could enhance polyclonal B-cell expansion with increased immune complex formation resulting in clinically significant vasculitis in genetically susceptible individuals [159].

MIS-A was reported in three patients within three to fourteen days after COVID-19 vaccination; one of them presented with shock. The three patients had underlying comorbidities such as asthma, depression, and hyperlipidemia[160]. Mild myocarditis was reported in six male patients between 16 and 49 years from Israel following BNT162b2 mRNA COVID-19 vaccination. Five presented one to three days after the second dose, while only one presented after 16 days from the first dose. All of them completely recovered within 4-8 d[161]. Autoimmune thyroid diseases (subacute thyroiditis and Graves' disease) were reported in a few persons following SARS-CoV-2 vaccinations, which could be a form of adjuvants-induced autoimmune/inflammatory syndrome (ASIA). Subacute thyroiditis and Graves' disease had developed in the reported cases within a few days following SARS-CoV-2 vaccination. ASIA was the underlying mechanism for several autoimmune endocrinopathies that developed after vaccination[150,162,163]. An *et al*[164] reported reactive arthritis in the left knee in a 23-year female; three days following the first and second doses of Sinovac-CoronaVac COVID-19 (inactivated whole virus) vaccine. She has a history of a similar condition two years before following a common cold which may indicate the genetic susceptibility of this patient.

Autoimmune hematological disorders were also observed following COVID-19 vaccination. Lee *et al* [165] reported that twenty patients between 22 and 73 years old developed immune thrombocytopenia and bleeding without thrombosis following Pfizer and Moderna SARS-CoV-2 (mRNA) vaccination. These patients tested positive for anti-platelet antibodies; some have other autoimmune conditions such as Crohn's disease or autoimmune hypothyroidism. Meanwhile, Cines *et al*[166] analyzed three independent reports describing 39 persons who developed immune thrombotic thrombocytopenia following the AstraZeneca COVID-19 vaccine (vaccine with modified recombinant adenovirus to encode SARS-CoV-2 S protein). Most patients had high antibody titer against platelet factor 4–polyanion complexes. Fourty% of the patients died from a cerebral hemorrhage, infarction, or both. Fatima *et al*[167] reported a 66-year-old woman who developed IgG-mediated autoimmune hemolytic anemia after Moderna COVID-19 (mRNA) vaccine. The patient had a history of psoriasis for five years before the vaccination.

Gaignard *et al*[168] also reported 77-year- males without previous comorbidities who developed autoimmune hemolytic anemia due to warm antibodies following Moderna COVID-19 (mRNA) vaccine. Brito *et al*[169] reported severe autoimmune hemolytic anemia in an 88-year-old Caucasian woman two days after the second dose of the COVID-19 mRNA vaccine. She had very high levels of anti-erythrocyte IgG and anti-C3d autoantibodies but without cold agglutinins. Murdych also reported severe autoimmune hemolytic anemia in an 84-year-old man with multiple comorbidities after the first dose of the Pfizer-BioNTech COVID-19 mRNA vaccine. The patient tested positive for direct antiglobulin, anti-IgG, direct antiglobulin, polyspecific antihuman globulin, and negative anti-C3[170]. There are several other reports of autoimmune hepatitis following mRNA or viral vector COVID-19 vaccines. Drug-induced hepatitis was also reported following the inactivated whole virus vaccine[171].

Neurological side effects of the COVID-19 vaccine are usually mild. However, severe adverse autoimmune neurological sequelae were reported. Waheed *et al*[172] reported GBS in an 82-year-old highly functional woman without significant comorbidities 14 d after the first shot of the Pfizer COVID-19 vaccine. She was successfully treated with IVIG. Other neurological complications such as Bell's palsy, acute transverse myelitis, acute demyelinating polyneuropathy, and transverse myelitis were reported, especially with mRNA vaccine[173]. Cerebral venous sinus thrombosis was also described in women of childbearing age, especially with adenovector-based vaccination[174]. The importance of developing vaccine-related autoimmune reactions or diseases is related to their impact on the intake of second dose vaccination and the morbidity rate. However, being cautious is preferable until reliable data and a more extended experience are established[175]. It is also essential to be highly suspicious when reporting vaccine-related side effects and rule out actual SARS-CoV-2 infection.

EFFECTS OF AUTOIMMUNE DISEASES ON THE COURSE OF COVID-19

Patients with immune deficiencies or autoimmune disorders are at a higher risk for infection with COVID-19, as they are frequently treated with anti-cytokine, glucocorticoids, and/or immunosuppressive drugs. The infection rate with COVID-19 among people with immune diseases is twice that of the general population[176]. The data derived from international registries of patients with rheumatic diseases (C19-GRA3) who encountered COVID-19 showed poor outcomes depending on their medications[177]. For example, patients treated with antitumor necrosis factor (TNF) showed decreased hospitalization risk, indicating the protective effects of anti-TNF monotherapy against severe COVID-19. Antimalarial drugs (such as hydroxychloroquine), non-steroidal anti-inflammatory drugs, and biologic therapies were not related to increasing the risk of hospitalization due to COVID-19. In contrast, patients who received moderate to high dose glucocorticoids had poor prognoses and clinical outcomes[177,178]. However, other factors may also play a role in the clinical outcome that need more studies.

Meanwhile, the study by Gianfrancesco *et al*[179] showed that most patients with autoimmune disorders who encountered COVID-19 had entirely recovered from the infection, which could help assure these patients. A meta-analysis by Akiyama *et al*[176] showed that while patients with autoimmune disorders have an increased prevalence of COVID-19, their prognosis and clinical outcome were not significantly worse than individuals without autoimmune diseases. They related the higher rate of COVID-19 in patients with an autoimmune disorder to the increased rate of glucocorticoid use. A recent study by Malek Mahdavi *et al*[180] showed that the presence of other comorbidities (female gender, obesity, hypertension, cardiac disease, diabetes mellitus, pulmonary disease, and chronic renal disease) in patients with rheumatoid arthritis in addition to treatment with prednisolone > five mg/day and TNFα inhibitors were independent predictors of COVID-19 outcome. They also observed that symptoms such as anosmia, dyspnea, and taste loss were more common than in the general population. When comparing the effects of COVID-19 with influenza on patients with autoimmune diseases, Tan *et al*[181] found that the hospitalized patients due to COVID-19 had poor outcomes and higher mortality rates than with influenza. However, this study had many limitations, so we can not generalize their findings. Both autoimmune disease and COVID-19 are known to increase the risk of venous thromboembolism. Consequently, the co-occurrence of COVID-19 in patients with autoimmune diseases may heighten this risk. D'Silva *et al*[182] found that patients with autoimmune disorders had a higher risk of venous thromboembolism when infected with SARS-CoV-2 than the general population, independent of comorbidities.

Factors affecting the severity Of COVID-19 in patients with autoimmune diseases

Table 4 summarises the factors that affect the severity of COVID-19 in patients with autoimmune disorders. The male sex and old age worsen the prognosis in patients with autoimmune diseases, similar to what is observed in the general population[183]. Freites Nuñez *et al*[184] indicated that age over fifty is an independent risk factor for hospitalization due to COVID-19 in patients with autoimmune diseases. Peach *et al*[185] found that the COVID-19-related mortality risk is higher in patients with autoimmune diseases with age equal to or higher than 35 years. They also showed that women with autoimmune diseases have a higher COVID-19-related mortality rate than men, contrary to the previous studies. The type of autoimmune disease can affect the severity of infection with SARS-CoV-2. For example, patients with SLE are at higher risk of severe COVID-19 than patients with rheumatoid arthritis. Patients with SLE may have a high rate of hypomethylation and ACE2 overexpression that may ease the viral entry into the cell[186].

On the other hand, Ayala Gutiérrez *et al*[183] found that patients with rheumatoid arthritis, polymyalgia rheumatica, vasculitis, and spondyloarthropathies had a worse prognosis; In comparison, patients with primary Sjögren syndrome and systemic sclerosis had a better prognosis. The presence of medical comorbidities (such as diabetes, hypertension, and obesity) in patients with autoimmune disorders increases the probability of hospitalization, intensive care unit (ICU) admission, and acute renal failure when they encounter SARS-CoV-2 infection[182]. The type of medication used can alleviate or worsen the course of COVID-19. Some drugs used to treat autoimmune diseases (such as Tocilizumab, Anakinra, Baricitinib, or hydroxychloroquine) might have a preventive effect in patients with severe COVID-19 infections. This finding may illustrate the underlying pathogenetic relationship between COVID-19 and autoimmune diseases[187]. Patients with autoimmune diseases treated with rituximab may be at greater risk of severe SARS-CoV-2-induced pneumonia than the general population [188]. Disruption of the medical care continuity and lack of medication adherence due to the restrictions during the pandemic may make the patient prone to flare-up and worsen the associated autoimmune disease activity[189].

Table 4 Factors that affect the severity of coronavirus disease 2019 in patients with autoimmune diseases

The age and sex of the patients
The type of the autoimmune disease
The severity of the autoimmune disease.
Presence of comorbidities
The type of medication used
Disruption of the medical care continuity
Lack of medication adherence
Other factors that increase COVID-19 severity in the general population

COVID-19: Coronavirus disease 2019.

CONCERN ABOUT COVID-19 VACCINATION IN PATIENTS WITH AUTOIMMUNE DISORDERS

The immunogenicity and safety data of COVID-19 vaccines are still limited because patients with chronic diseases, including autoimmune diseases and immunosuppressed patients, were excluded from most experimental vaccine studies. Patients with autoimmune diseases are more liable for a more severe and complicated course of COVID-19 than the general population. Hence, the vaccination benefits far outweigh the risks[190]. According to the general vaccination guidelines in patients with immune deficiency or autoimmune diseases, giving these patients non-live vaccines (including mRNA vaccines) is recommended, providing adequate cellular and humoral immune response. It is preferable to give these patients the immunization during the disease's remission and without concurrent infections[191].

Patients on high doses of corticosteroids or Rituximab may avoid the vaccination. Preferably, COVID-19 vaccinations should be given before initiating any biological disease-modifying agents. Patients may receive the COVID-19 vaccine one month before or at least six months after the last Rituximab infusion, as Rituximab impairs the antibody responses for at least six months after administration[192]. Patients with autoimmune diseases or immune deficiency should receive annual influenza and Streptococcus pneumonia vaccination. COVID-19 vaccine should be given alone and at least two weeks before or after other vaccines. Coordinating timing with dosing regimens of COVID-19 vaccines may optimize the vaccine safety and efficacy, especially in patients with autoimmune diseases[193].

WAYS TO MINIMIZE THE RISK OF COVID-19 IN PATIENTS WITH AUTOIMMUNE DISEASES

Patients with autoimmune diseases are more liable to nutritional inadequacy due to the effects of the disease itself or related to the medications used. The nutritional inadequacy may increase the susceptibility to infection, especially to COVID-19, and permit infections to be more serious, even fatal[194]. Immune-regulator micronutrients such as vitamin A, D, and zinc are essential for immune cell metabolism and may provide antibacterial or anti-viral effects. Other micronutrients such as arginine may be needed as substrates for immune-active metabolites production, such as nitric oxide, one of the most crucial players in immunity[195]. Vitamin D decreases the risk of respiratory tract infections and other respiratory disorders. It is better to be taken daily to obtain maximum effects[196,197]. Vitamin E, Vitamin C, selenium, zinc, plant polyphenols, and long-chain omega-3 fatty acids have anti-oxidative effects and protect against inflammatory stress[198]. Adequate nutrition is essential for healthy gut microbiota, which plays a fundamental role in immunity modulation[199]. Several studies showed the efficacy of probiotics in gut microbial modification, improving gastrointestinal manifestation, and reducing multiorgan inflammation in different autoimmune diseases[200,201]. Licorice is a traditional herb used as a drink in Egypt for many centuries. It has many beneficial effects, such as anti-inflammatory, antitussive, antibacterial, immunomodulatory, and detoxifying agents for many disorders, especially respiratory diseases. It has a solid potential to be an effective adjuvant to prevent and treat COVID-19 with significant anti-inflammatory, anti-ACE2, and the ability to alleviate the clinical symptoms of the disease such as dry cough, shortness of breath, and fever[63].

Gut microbiota is an essential determinant of immunity. COVID-19 causes disruption of the intestinal flora and microbiota dysbiosis, which induces Th17 cell polarization in the small intestine with excessive interleukin (IL)-17A production, recruitment of neutrophils, and more intestinal mucosal immune damage[202]. Several studies highlighted the pathogenetic prole of the microbiome in the

development of autoimmune diseases, especially in systemic lupus erythematosus. Peng *et al*[203] showed that probiotics successfully adjunctive therapy in SARS-CoV-2 infection[204]. Consequently, improving the host nutrition and general condition increases the ability to fight infection and enhances the vaccination response. Alcohol consumption and smoking should be avoided during the COVID-19 pandemic, particularly in patients with autoimmune diseases. Alcohol exacerbates intestinal inflammation, alters intestinal microbiota's composition and function, increases intestinal permeability, and disturbs intestinal immune homeostasi[205]. Cigarette smoking impairs various body functions such as cardiovascular, respiratory, and immune systems and exacerbates autoimmune diseases and allergies. Smoking impairs the nuclear factor-kappaB (NFκB), mitogen-activated protein kinases, and histone modification. It also impairs innate and adaptive immunity and makes the smoker more prone to infection[206].

Sleep hygiene has a direct impact on immunity upkeep and immunological response. Disordered Circadian rhythm, due to physical, social, or psychological disorders encountered during the COVID-19 pandemic, compromises the sleep quality and hence the immune system. Good sleep quality improves the response to vaccination and increases the resistance to infectious diseases[207]. Poor sleep quality is associated with increased pro-inflammatory interleukin levels (IL-1β, TNF-α, and IL-6)[208]. Exercise during the COVID-19 pandemic promotes health, improves host immunity, and should be encouraged. Acute and chronic exercise of moderate intensity can control excessive respiratory inflammation through multiple pathways. It also enhances and regulates the immune defense mechanism, particularly innate immunity, and improves metabolic health[209].

The enforced social isolation and stress during the pandemic negatively affect individual health, especially in children and the elderly[210,211]. Social isolation and anxiety disturb the various biological systems and the circulating stress hormones, glutamate, and immune system components[212]. Social isolation also triggers neuroinflammation and microglia overactivation and disturbs gut microbiota, inducing various neurological and autoimmune disorders. Therefore, a multi-purpose comprehensive social and family program with exercise and psychological support is highly needed for patients with autoimmune diseases to lessen the harmful effects of social isolation impeded during the COVID-19 [213-219].

CONCLUSION

Mutual relations exist between COVID-19 and autoimmune diseases. Patients with autoimmune disorders are at an increased risk for COVID-19, and COVID-19 or its vaccine can trigger autoimmune diseases. Patients with autoimmune diseases should continue their medication but could be modified according to their clinical condition. Vaccination with non-living viruses, including mRNA, is safe and could prevent serious COVID-19. However, the COVID-19 vaccination could also trigger autoimmune disease. Consequently, precautions and strict follow-up are needed for these patients.

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Issues related to post-COVID-19 syndrome

Öner Özdemir, Zeynep Arslan

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Abstract

The pandemic caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) in 2019-2022 leads to a multisystem illness that results in damage to numerous organ systems. In this review, our goal was to assess current research on long-term respiratory, cardiac, neurological, digestive, rheumatological, urogenital, and dermatological system complications of coronavirus disease 2019 (COVID-19). Bibliographic searches were conducted in December 2021 using PubMed and Google Scholar, retrospectively, covering all COVID-19 literature to determine the consequences of the disease. This review may help to determine the prospects for new studies and predict the upcoming aspects requiring assessment in post-COVID-19 syndrome.

Key Words: Coronavirus; COVID-19; Post-COVID-19 syndrome; Pandemic; SARS-CoV-2

Core Tip: Coronavirus disease 2019 causes damage to multiple organ systems. Most of the current studies are based on the acute stage of illness, treatment, and vaccination. As more than two years have passed since the start of the pandemic, we should be familiar with its long-term sequelae.

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INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic, caused by acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has invaded the globe. As of 8 June 2022, the cumulative number of recorded infected cases is 536.613.318, with 6.323.467 deaths[1]. Although the pathophysiologic process remains unclear, a probable hypothesis suggests that SARS-CoV-2 is an enveloped and positive-stranded RNA virus that binds to the angiotensin-converting enzyme 2 (ACE2) receptor of host cells with the structural protein spike domain S1[2]. Consequently, the novel coronavirus invades all cells that express ACE2 receptors, such as respiratory, gastrointestinal, and urinary systems[3]. Studies have indicated that the incubation period may take up to 11.2 d, and symptoms of the disease are likely to be evident on day 5.5 after infection in most cases[4]. Additionally, current studies revealed that the average incubation period in the pediatric age group is 6.5 d, which is slightly longer than that in adults[5].

SARS-CoV-2 has additional features that most other organisms may not have: (1) Ability to escape immunological response; (2) Tissue tropism which depends on ACE2 receptor consistency; and (3) Capability to reach various organs and systems[6].

Common clinical manifestations in COVID-19 patients include fever, dry cough, fatigue, dyspnea, sore throat, headache, myalgia or arthralgia, chills, nausea or vomiting, nasal congestion, diarrhea, hemoptysis, and conjunctival congestion[7]. Another study involving pediatric participants demonstrated that 61.7% had a fever, 53.2% cough, and 16.8% diarrhea or nausea[8].

The aim of this mini-review was to conduct a bibliographic search of post-COVID-19 syndrome which was carried out in December 2021 using PubMed and Google Scholar, retrospectively, and included all COVID-19 literature to determine the consequences of this disease. This review may help to determine the prospects for new studies and predict the upcoming aspects requiring assessment in post-COVID-19 syndrome.

WHAT IS POST (LONG)-COVID-19 SYNDROME?

According to the studies that were conducted to assess hospitalization and mortality data, the majority of patients have the burden of long-term morbidity complications despite 'recovery'[9,10]. A group of patients had persistent complaints, which necessitated the need to determine long-term complications of the disease. Approximately 10% of the infected patient population reported experiencing symptoms such as confusion, sleep problems, decreased exercise capacity, autonomic complaints, persistent low-grade fever, and lymphadenopathy after recovery from the acute stage[11,12]. Another large cohort study including data from patients 6 mo after recovery showed that a considerable number of patients had persistent complaints of fatigue, muscle weakness, sleep difficulties, anxiety, and depression[13]. Severely ill patients with extensive lung involvement at admission was a probable risk factor associated with pulmonary diffusion abnormality, fatigue or muscle weakness, and depression which are manifestations of a new term called 'post-COVID-19 syndrome'[14]. These manifestations are reliant on the severity of pulmonary involvement, age, muscle pain, intensive care unit (ICU) requirement, viral load, and immune response at admission[15-17]. Obesity, underlying chronic respiratory illness, abnormal radiologic findings, diminished pulmonary function on spirometry, female gender, and Black and Asian races are also reported to be potential risk factors for long-term sequelae[18].

The novel terminology of 'COVID long-haulers', 'long-COVID', or 'post-COVID-19 syndrome' covers these complaints[10]. 'Acute COVID-19' describes symptoms that extend to 4 wk after the onset of the disease. On the other hand, the definition of 'post-acute COVID-19', is symptoms present between 4 to 12 wk after onset of the disease[19,20]. Post-COVID-19 syndrome or long-COVID consists of complaints that remain beyond 12 wk and are not associated with any other disease[19,20]. A study investigating children with persistent COVID-19 symptoms found that symptoms were present for 4 to 12 wk, and could even persist for 7 to 8 mo[21]. In this review, we use the term 'post-COVID-19 syndrome'.

Studies have shown that among symptomatic patients, 21.4% had profound symptoms even 20 wk after recovery[22]. The duration of COVID-19 and comorbidities (such as unstable diabetes mellitus, and hypertension) were found to be associated with post-COVID-19 syndrome[22]. Interestingly, the age group of 1-10 years had no complaints after recovery, but patients older than 40 years had remnant findings even 20 wk after onset[22].

Although current knowledge on symptomatic patients after discharge is insufficient, in order to have a comprehensive framework, studies that investigated post-COVID-19 syndrome have been included in this review (Table 1).

Respiratory system involvement

During the course of COVID-19, an important proportion of cases suffer from severe pneumonia and tend to have long-term sequelae[23]. Ongoing fibrosis during the recovery period results in decreased diffusion capacity of the lung[24]. Studies have indicated that a large variation in respiratory morbidity may appear such as decreased exercise capacity, an increased need for continuous positive airway pressure, tracheostomy, or ventilator dependence for COVID-19 long-haulers[13,24-27].

Table 1 Involvement of organ systems in post-coronavirus disease 2019 syndrome

Systems	Findings
Respiratory system	Decreased diffusion capacity of the lung due to ongoing fibrosis
	Decreased exercise capacity, cough, and chest pain
Hematologic system	CD4+- T lymphocytes remained lower
	Mild elevation in white blood cell (WBC) count
	High levels of WBCs are driven by raised neutrophils
	Direct injury of endothelium and cytokine release causing prothrombotic tendency
	Elevation of Von Willebrand Factor antigen (VWF: Ag), VWF propeptide (VWFpp), and Factor VIII coagulation (FVIII: C) elements
Cardiovascular system	Vascular, pericardial, and myocardial tissue inflammation
	Chest pain, palpitations, dizziness, and increment in resting heart rate
	Postural orthostatic tachycardia syndrome (POTS)
Gastrointestinal system	Diarrhea, abdominal pain, and nausea
	Viral RNA could still be present in the stool after 30 d
	Weight loss and risk of malnutrition due to decreased appetite
Neurologic system	Mild headache, hyposmia, hypogeusia, fatigue, sleep disorders, pain, cognitive impairment, and rarely Guillain-Barré syndrome
	Anosmia and hypogeusia, underlying low-grade inflammation of the frontal lobe, loss of cognition, brain fog, and headache
Psychiatric issues	Social withdrawal, social isolation, economic loss due to being unable to work, increased child care and familial charges, and burden of guilt if other contacts contract the virus
	Psychological distress and post-traumatic stress disorder

The up-to-date pathophysiological process of lung fibrosis development in COVID-19 includes pulmonary consolidation, hyaline membrane formation, capillary damage and bleeding, diffuse alveolar epithelium destruction, and alveolar septal fibrous proliferation[28]. A cohort study reported that more than 50% of patients with SARS-CoV-2 pneumonia at 30 d post-infection had abnormal results for functional residual capacity, total lung capacity, and diffusing capacity of the lungs[29]. Although, pulmonary fibrosis occurs in most patients it was reversed in less than half of the patients 3 mo after onset[30].

Myall *et al*[31] conducted a cohort study that included 837 COVID-19 patients. The patients were screened *via* phone calls 4 wk after discharge. 325 patients had ongoing symptoms. Following assessment of this group using various tests [chest X-ray, 6-min walking, echocardiogram, and computed tomography (CT)], 35 (4.18%) patients were diagnosed with interstitial lung involvement, and were successfully treated with corticosteroids. The main characteristics of the group with lung involvement were being male, obese, in need of oxygen therapy, and mechanical ventilation during the acute phase.

In a study conducted to highlight long-term respiratory results, 244 patients required prolonged ICU and inpatient stay, and follow-up chest X-rays. Of these patients, 23 (9%) showed significant deterioration 2 mo after onset of the disease[32]. To evaluate the relationship between radiological involvement at admission and impaired lung function, a prospective cohort study was conducted. Patients who presented with acute respiratory distress syndrome (ARDS) during ICU stay resulting from COVID-19 were included in the study and examined *via* chest CT and pulmonary function tests 3 mo after discharge. Pulmonary function tests were abnormal in 55% of patients, with restricted diffusing capacity of the lungs[33]. In a large study of more than 4000 COVID-19 survivors, risk factors for 90-d mortality were reported as older age, immunosuppression, severe obesity, diabetes, higher renal and cardiovascular sequential organ failure assessment (SOFA) score components, lower PaO2/FiO2 ratio and a shorter time between first symptoms and ICU admission[34].

CT changes in post-COVID-19 syndrome provide information on long-term pulmonary effects. A study that included 52 subjects with COVID-19 assessed *via* CT 3 mo after diagnosis showed that 22 (42%) patients had residual findings. Problems with decreased lung capacity, cough, and chest pain were more common among patients with abnormal CT scans[35].

Cardiovascular system involvement

A history of pre-existing cardiovascular illness or hospitalization were not associated with post-acute-COVID-19 syndrome (PACS)[36]. Before the pandemic, it was hypothesized that the density of ACE2 receptors in the heart was due to myocardial injury. However, recent studies demonstrated that the

cause of type 2 myocardial infarction was increased systemic inflammation[37]. Vascular, pericardial and myocardial tissue inflammation yields typical cardiac complaints of chest pain, palpitations, dizziness, and an increment in resting heart rate[25,38].

A cohort study was performed by Puntmann *et al*[39] to determine myocardial inflammation rates in patients with a history of COVID-19 infection. The patients were analyzed 2 wk after hospital discharge by cardiac magnetic resonance (CMR) imaging to evaluate myocardial involvement. A control group was also included to investigate similar risk factors to the study group. The study group subjects were found to have significant T2 signal and late gadolinium enhancement. Another study of 148 patients with elevated troponin levels during hospitalization were followed up for 2 mo after discharge. It was reported that 26% of the patients developed a myocarditis-like pattern, while all patients had normal left ventricle function. Active myocarditis with regional elevation in T1 and T2 signals was demonstrated in 8% of patients. However, elevated troponin was not found to be predictive of myocarditis[40]. In a multicenter study, almost 20,000 athletes following recovery from COVID-19 were examined and only 3% of them were found to have possible pathology 113 d after onset of the disease [41]. It may be inferred from recent studies that myocarditis is a very rare condition, especially in asymptomatic and mild cases.

In another study, 59 patients following hospitalization due to COVID-19 were screened *via* CMR imaging. One patient's imaging data indicated pericarditis[42]. Other research demonstrated that 5% of patients were estimated to have mild pericardial effusion[43]. Although further investigations are required, it can be inferred that pericarditis after COVID-19 is rare, while effusion is a relatively more common pathology.

Postural orthostatic tachycardia syndrome (POTS) is another disorder seen in a considerable number of COVID-19 long haulers. To estimate the incidence of this condition, 28 patients with persistent cardiac complaints after COVID-19 recovery were enrolled in a study. The results of the tilt table and ten minutes-standing tests demonstrated that 20 patients (70%) had POTS[44].

Arrhythmias after COVID-19 are quite rare and investigations on this issue are scarce. An analysis of arrhythmias in 5000 patients hospitalized with COVID-19 and influenza was carried out. Similar percentages of atrial fibrillation and atrial flutter were detected in both groups[43].

Hematologic system involvement

Laboratory markers for predicting the severity of disease and mortality have been questioned. It is known that several changes occur during the course of COVID-19. A study of 1099 reverse transcriptase-polymerase chain reaction (RT-PCR) positive patients demonstrated lymphocytopenia (83.2%), thrombocytopenia (36.2%), and leukopenia (33.7%) in the initial phase of the disease[45]. A few studies have investigated hematological findings after recovery. In a study of 313 participants, 12.9% of patients had leukocytosis, which increased to 16.1% 4 wk after recovery. The percentage with neutrophilia in the initial phase was found to be 17.7%, which increased to 33.8% and lymphocytopenia decreased from 17.7% to 14.5%. Almost half of the patients had increased D-dimer levels in the acute stage, which decreased to 6.4% after 1 mo[22].

Lymphopenia is a common finding in patients with COVID-19 and represents a defective immune response to the virus[1]. Cytotoxic lymphocytes such as cytotoxic T lymphocytes (CTLs) and natural killer (NK) cells have a main role in the control of infection. During the acute phase of the disease, both CTLs and NK cells decrease in number. However, after recovery, these cell numbers then increase. Hence, Zheng *et al*[46] suggested that the recovered numbers of these cells may predict convalescence.

Studies investigating the prevalence of lymphopenia in COVID-19 positive patients have provided different estimates ranging from 63% to 75%[47,48]. In patients with severe disease, a decrease in both CD4 and CD8 cells was noted. Additionally, lymphocyte count, especially CD4, may predict severity and prognosis[49]. A prospective study showed that CD8+- T lymphocytes recovered to their normal level 3 mo after onset of the disease. Another finding in this study showed that CD4+- T lymphocytes remained lower than in the healthy population even 4 wk after onset[50].

A large comprehensive meta-analysis of hematologic laboratory data demonstrated that patients with serious disease had a mild elevation in white blood cell (WBC) count. Additionally, patients who died due to COVID-19 had a significant increase in WBCs. According to this finding, WBC levels signify the severity of the disease. Despite reduced lymphocyte, monocyte, and eosinophil counts; high levels of WBCs were driven by raised neutrophils[49]. Similarly, recent research demonstrated that increased neutrophil/lymphocyte and peak thrombocyte/lymphocyte counts may help predict prognosis[51].

Thrombocytopenia in COVID-19 patients may be caused by disseminated intravascular coagulation, sepsis, or drug-induced, which was also shown to be a risk factor for increased morbidity and mortality [52]. Several studies have reported late-onset immune thrombocytopenia 4 wk after the onset of COVID-19[53].

A new description of the immune thrombotic state is termed COVID-19-induced coagulopathy[54]. A possible mechanism responsible for this prothrombotic tendency is the direct injury of endothelium and cytokine release which activates the coagulation cascade[55]. A cohort study screened 50 patients for endotheliopathy 68 d after recovering from COVID-19. This study showed that endothelial biomarkers von Willebrand Factor antigen (VWF: Ag), VWF propeptide (VWFpp), and Factor VIII coagulation (FVIII: C) elements were significantly elevated in post-acute-COVID-19 patients. Endothelial damage

may be a possible explanation for the pathogenesis of long-COVID-19 syndrome[56].

Post-discharge thromboprophylaxis has been assessed in post-COVID-19 patients. A prospective cohort study of 146 patients showed that 6 wk after discharge, while the percentage of thrombotic events was 0.7%, 30% of patients had increased D-dimer values[57]. Although there are ongoing studies to determine the rates of thrombotic events after COVID-19, routine thromboprophylaxis after discharge is not recommended. The Global COVID-19 Thrombosis Collaborative group recommends prophylaxis for selected patient groups only such as the elderly population and those with existing comorbidities [58].

Gastrointestinal system-related issues

SARS-CoV-2 mainly leads to diseases associated with the respiratory tract, but gastrointestinal disturbances can also occur. During the natural course of the disease, patients develop anorexia, nausea, vomiting, and diarrhea[47]. In contrast to early studies that suggested lower rates of diarrhea and other digestive symptoms, recent data show that almost half of patients have gastrointestinal system complaints[59,60]. A large cross-sectional study including 979 participants who recovered from COVID-19 demonstrated that almost half of the patients had diarrhea, abdominal pain, and nausea[61]. The appearance of digestive system complaints is delayed, compared to respiratory symptoms and begin at about 9.0 d[62]. Although there are numerous reports regarding gastrointestinal involvement during the acute stage, the effects of post-COVID-19 syndrome on the digestive system remain unclear.

Viral shedding from the gastrointestinal tract may be massive and continue long after the resolution of clinical signs[63]. A study on SARS-CoV-2 demonstrated that viral RNA could remain in the stool even after 30 d[64]. More than half of the patients were found to have viral RNA in their stool during the acute stage of disease, and one in five patients had positive stool samples even after viral RNA was eliminated from their airways[59]. Another investigation which assumed that SARS-CoV-2 spread *via* the stool displayed similar conclusions showing that virus shedding continued even after the convalescent phase of the disease. It was also suggested that viral RNA in feces detected by RT-PCR can be used to monitor infection[65].

Early data suggested that higher numbers of ACE2 receptors in cholangiocytes (59.7% of cells) compared to hepatocytes (2.6% of cells) show that the virus may be directly attached to ACE2-positive cholangiocytes and damage liver function[66]. Nevertheless, autopsy studies reported no viral inclusion in the liver[67]. Correspondingly, an overactive inflammatory reaction may be responsible. The underlying mechanism can be explained as follows: Typical lymphopenia detected in SARS-CoV-2 infection causes increased serum levels of interleukin-6 (IL-6), IL-10, IL-2, and interferon (IFN)-γ which may damage liver tissue[68]. Likewise, a strong association between lymphopenia and increased serum C-reactive protein level with liver injury has been proposed[69].

Studies on COVID-19 patients after remission indicate that weight loss and risk of malnutrition were highly prevalent 3 wk after recovery. Increased inflammation leads to decreased appetite. A prospective cohort study aiming to understand the long-term results of malnutrition in post-COVID-19 syndrome was carried out, and included 288 hospitalized COVID-19 patients who were followed up for 6 mo. On day 30, 136 (47.2%) patients had persistent malnutrition or sarcopenia. Gérard *et al*[70] found that the time taken to regain weight was 6 mo, but all patients generally remained 1.4 kg lighter than their weight on admission.

Urinary system involvement

An increased numbers of urinary frequency complaints have prompted the question: "Does SARS-CoV-2 infection cause viral cystitis?"[71]. The existence of viral RNA in the urine of COVID-19 sufferers showed that the urinary tract is potentially affected throughout the disease[45,72]. Ischemic and/or toxic tubular damage was detected in more than 14% of acute kidney injury (AKI) cases with COVID-19 [73]. The greater number of AKI patients with COVID-19 was related to acute tubular injury. The probable mechanism of acute tubular damage may involve volume reduction that reduces kidney perfusion. Another possible explanation is that the immune response produces cytokines that affect renal circulation[74]. There are no available data on the long-term complications of SARS-CoV-2 infection in the urinary tract.

Neurologic system involvement

Several studies have reported a large number of neurologic disorders ranging from mild headache, hyposmia, hypogeusia, and fatigue to sleep disorders, pain, cognitive impairment, and rarely Guillain-Barré syndrome[40]. To ascertain the main cause of neurological disorders, it is necessary to define the components of neuro-COVID, which tends to cause more disabling disease[6,75]. In patients with or without neurological manifestations during the acute phase of COVID-19, the cytological and biochemical study of cerebrospinal fluid, as well as neuroimaging, revealed significant alterations that represented inflammatory activity. It was also noted that during the acute phase of the disease, a consequential number of inflammatory events were demonstrated by radiological surveys of the central nervous system and both cytological and biochemical evaluations of cerebrospinal fluid[76].

To shed light on the neurological disturbances after COVID-19, it is essential to know the tropism of the virus and how it accesses the nervous system. The nasal and oral cavities provide an area for seeding of SARS-CoV-2. From the olfactory mucosa *via* retrograde neuronal transport, the virus reaches the central nervous system[77]. The inflammatory response of nasal and oral mucosa may be the reason for anosmia and hypogeusia. Moreover, as anosmia and hypogeusia have a similar mechanism, underlying low-grade inflammation of the frontal lobe might be the cause of the loss of cognition, brain fog, and headache[77]. As silent target organ damage and underdiagnosis of post-COVID syndrome results in neurological manifestations, taking precautions with regard to initial neurorehabilitation is essential[78].

There are a considerable number of reports of patients with demyelinating pathologies such as Guillain-Barre syndrome, Miller-Fisher, and other inflammatory polyneuropathies. A review of these cases showed that symptomatic neuropathy may be diagnosed 3 to 33 d after onset. The absence of SARS-CoV-2 RNA in the cerebrospinal fluid indicates that a post-infectious process is thought to be responsible rather than a para-infectious process[79]. There is another case report of status epilepticus and hippocampal atrophy due to prolonged inflammation 6 wk after SARS-CoV-2 infection[80]. Another patient with orthostatic cerebral hypoperfusion syndrome and painful small fiber neuropathy after recovery has been reported[81].

The most commonly reported neurological disturbance in COVID-19 patients is headache (18%-38%) [82,83]. Other complaints consist of peripheral neuropathy symptoms, tinnitus, memory issues, concentration, and sleep disturbances[84].

Psychiatric issues

The psychological health outcomes during COVID-19 recovery may contribute to social withdrawal, social isolation, economic loss due to being unable to work, increased child care and familial charges, and burden of guilt if other contacts contract the virus[85]. Nonetheless, patients with SARS-CoV-2 heal physically; however, they are prone to psychological distress and post-traumatic stress disorder. A study showed that more than half of patients had these mental disorders after surviving severe disease [86]. The first study on the neuropsychological findings of post-COVID-19 patients showed that the Beck Depression Inventory scores were significantly higher in post-COVID-19 patients than in healthy controls[87].

Endocrinological involvement

The impact of post-COVID syndrome on the endocrine glands cannot be underestimated. Symptoms such as tiredness, weakness, nausea, diarrhea, dizziness, and joint pain may overlap with adrenal insufficiency symptoms. For instance, Salzano *et al* reported a patient with adrenal insufficiency following recovery from SARS-CoV-2 infection[88]. Additionally, a cohort study of 453 patients was conducted and thyroid-stimulating hormone (TSH) and thyroxine (T4) levels before, during, and after SARS-CoV-2 infection were evaluated. According to this study, while most cases were found to be euthyroid, a slight decrease was reported in both TSH and T4 levels, which normalized after infection [77].

Dermatological issues

A single-center prospective study to define the skin manifestations of long COVID syndrome in 104 patients was conducted by Diotallevi *et al*[89]. Following hospital discharge, the patients were followed up at 1, 3, and 6 mo and examined by dermatologists who reported a wide spectrum of findings such as telogen effluvium, skin xerosis, diffuse folliculitis, vesicular exanthema, relapse of seborrheic dermatitis, relapse of psoriasis and pityriasis versicolor. According to the study, telogen effluvium due to interruption of the anagen phase was the most prevalent dermatological finding in patients after SARS-CoV-2 infection.

CONCLUSION

As the new coronavirus, SARS-CoV-2, involves multiple organ systems and the number of COVID-19 survivors increases every day, there is a need to develop new strategies for the systematic assessment of these patients as well as the need for rehabilitation services. Multidisciplinary post-acute COVID-19 care services should include several specialists to evaluate the consequences of the disease, and highlight some of the unrecognized disorders of COVID-19.

FOOTNOTES

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MINIREVIEWS

Rehabilitation in long COVID-19: A mini-review

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Abstract

We have been experiencing multiple waves of the coronavirus disease 2019 (COVID-19) pandemic. With these unprecedented waves, we have entered into an era of 'new normal'. This pandemic has enforced us to rethink the very basics of childhood learning: Habits, health etiquette, and hygiene. Rehabilitation has immense importance during this pandemic considering a few aspects. Multidisciplinary COVID-19 rehabilitation clinics are essential to address the demand. The equitable distribution of COVID-19 rehabilitation services for differently-abled individuals during the pandemic is an important aspect. Rehabilitation needs identification and further studies on various rehabilitation interventions are among the key unmet future research needs.

Key Words: COVID-19; Long COVID-19; Post-COVID-19 syndrome; Rehabilitation; SARS-CoV-2; Long haulers

Core Tip: The coronavirus disease 2019 (COVID-19) pandemic has impacted negatively on multiple systems of our body, among them the pulmonary system is the most pronounced. The cardiac, nervous, and musculoskeletal systems are also involved. Post-COVID-19 especially post-intensive care unit or post mechanical ventilation and long-COVID-19 can cause significant functional loss and disability. Rehabilitation has an immense role to bring back the achievable functional status of COVID-19 patients. Multidisciplinary COVID-19 rehabilitation clinics are essential to address the demand. The equitable distribution of COVID-19 rehabilitation services for differently-abled individuals during the pandemic is an important aspect. Rehabilitation needs identification and further studies on various rehabilitation interventions are among the key unmet future research needs.

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INTRODUCTION

We have been experiencing multiple waves of the coronavirus disease 2019 (COVID-19) pandemic. With these unprecedented waves, we have entered into an era of 'new normal'. This pandemic has enforced us to rethink the very basics of childhood learning: Habits, health etiquette, and hygiene. It taught us the importance of each stage of prevention: Primordial, primary (mask, sanitization, social distancing, and vaccine), secondary (treatment, critical care, and rehabilitation in acute care), tertiary (disability limitation and rehabilitation), and quaternary (prevent treatment side-effects) (Figure 1). On the other hand, it became a tragedy for people who lost their near and dear ones and those who lost their financial support/job. When we say rehabilitation, it must be emphasized that we should consider the person as a whole rather than the disease. Rehabilitation is defined as "a set of interventions designed to optimize functioning and reduce disability in individuals with health conditions in interaction with their environment".

Coronaviruses are single-stranded RNA viruses that cause respiratory, gastrointestinal, and neurological diseases. The first coronavirus - severe acute respiratory syndrome coronavirus (SARS-CoV) - was thought to originate in Foshan, China and resulted in the SARS-CoV pandemic (2002-2003). The second coronavirus caused Middle East respiratory syndrome, which originated from the Arabian Peninsula in 2012. SARS-CoV-2 started in Wuhan, Hubei Province, China in December 2019. On January 12, 2020, the World Health Organization (WHO) named it novel coronavirus (2019-nCoV) and officially named it 'COVID-19' on February 11 2020, and finally the International Committee on Taxonomy of Viruses officially designated the virus as SARS-CoV-2. On January 20, 2020 human-to-human transmission was confirmed. On 11 March 2020, WHO declared it as a 'pandemic'. On March 18, 2020, the WHO and partners launched the Solidarity trial, an international clinical trial aimed 'to generate robust data from around the world to find the most effective treatments for COVID-19'.

Till now, globally more than 298 million confirmed cases (in India: > 35 million) and 5.4 million (in India: > 0.4 million) deaths have been recorded.

Causative agent

COVID-19 is caused by SARS-CoV-2. SARS-CoV-2 is enveloped and spherical shaped (120 nm), having a positive-sense single-stranded RNA genome[1]. It belongs to the subfamily Orthocoronavirinae (family: Coronavirdiae; order: Nidovirales) and is classified as a beta-coronavirus [lineage B]. The name corona came from a crown-like appearance under an electron microscope ('coronam' is the Latin word for 'crown') due to the presence of spike glycoproteins on its envelope. The spike glycoprotein of SARS-CoV-2 binds to angiotensin-converting enzyme 2 (ACE2) in humans for cellular entry. Till now, five variants of concern have been identified: Alpha (B.1.1.7); Beta (B.1.351); Gamma (P.1); Delta (B.1.617.2); Omicron (B.1.1.529).

Bat [horseshoe bats (*Rhinolophus* spp)] is the probable natural host and pangolins are considered an intermediate host[1].

Incubation period

2-14 d (mostly 5 d).

Mode of transmission

Primarily by respiratory droplets but airborne transmission is also implicated especially following aerosol-generating procedures. Fomite transmission also has been well characterized.

Clinical features

Fever (83%-99%), cough (59%-82%), and fatigue (44%-70%) are the frequent symptoms but anorexia (40%-84%), shortness of breath (31%-40%), myalgia (11%-35%), and diarrhoea (2%-38.1%) are also seen. Loss of smell (anosmia) or loss of taste (ageusia) is also reported in many cases. Most of the cases are having mild symptoms, and people with comorbidities and older age groups are particularly prone to develop severe disease.

Clinical severity

The WHO classified COVID-19 as mild, moderate (pneumonia), severe (severe pneumonia), and critical (acute respiratory distress syndrome, sepsis, and septic shock).

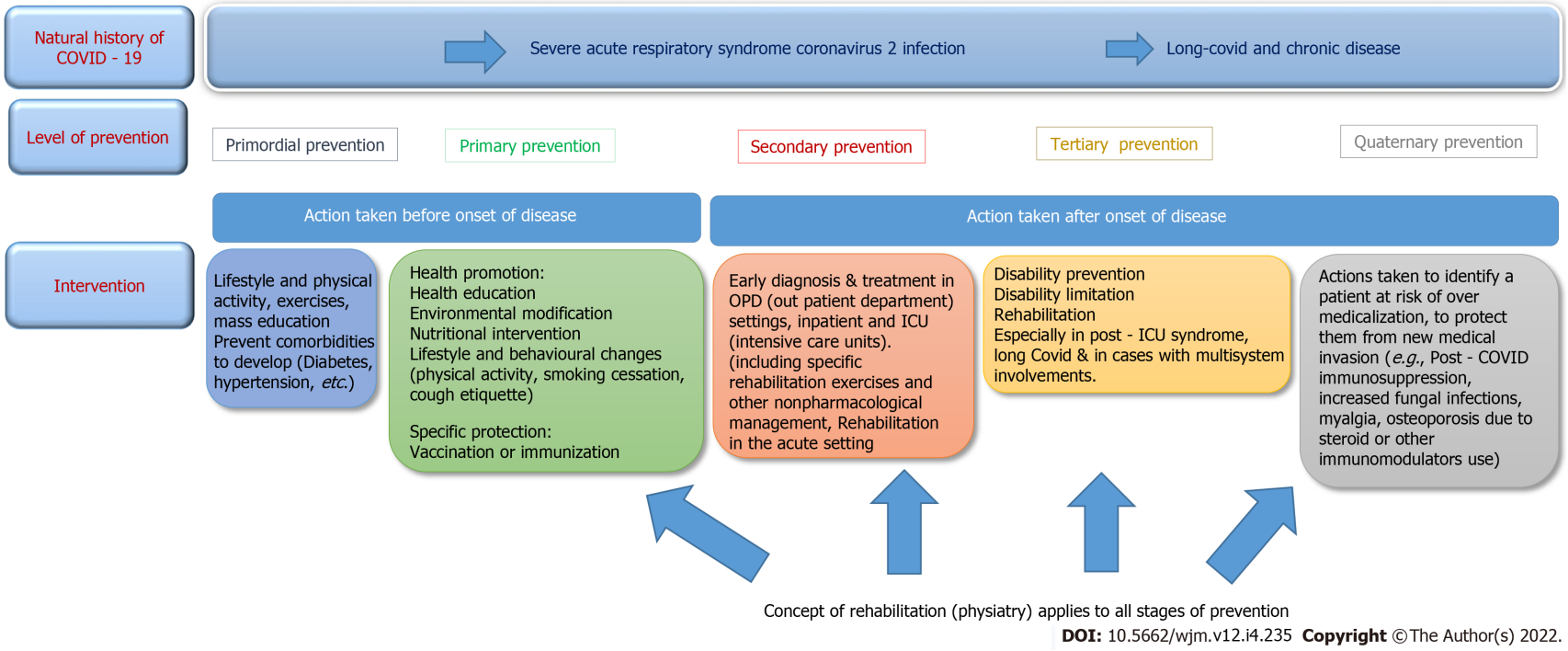

Figure 1 Rehabilitation perspective of the coronavirus disease 2019. COVID-19: Coronavirus disease 2019; ICU: Intensive care unit.

Pathophysiology

After entry into the cell, this virus causes diffuse alveolar damage in the lungs. Excessive immune reaction to the virus, causing cytokine storm, is mainly responsible for the clinical severity of COVID-19. The predominant mechanisms of acute COVID-19 include the following: Direct viral toxicity; endothelial and microvascular damage; dysregulated immune system; hypercoagulability; and maladaptation of the ACE2 pathway.

Investigation

Confirmation is done by real-time polymerase chain reaction using the upper and lower respiratory tract samples. Faecal specimens at times can be used as a sample. SARS-CoV-2 antibody testing is not recommended for diagnosis. Lymphopenia is a cardinal feature. Chest X-ray shows bilateral infiltrates, and high resolution computed tomography (HRCT) scan of the thorax shows ground-glass appearance as the most common finding.

COVID-19 confirmed case definition (WHO)

A person with laboratory confirmation of COVID-19 infection is regarded as a COVID-19 confirmed case.

According to ICD 11, the code for the confirmed diagnosis of COVID-19 is RA01.0 and for the clinical diagnosis (suspected or probable) of COVID-19 is RA01.1; the code for post-COVID-19 condition is RA02.

LONG COVID

The Centres for Disease Control and Prevention defined 'post-COVID conditions' as "a wide range of new, returning, or ongoing health problems that people can experience four or more weeks after first being infected with the virus that causes COVID-19"[2]. It is called long COVID/long-haul COVID/post-acute COVID-19. Common long COVID-19 symptoms are fatigue, arthralgia, breathlessness, cough, loss of smell, chest pain, palpitation, anxiety/depression and sleep disturbances, difficulty in concentration, *etc.*

In the National Institute for Health and Clinical Excellence guidelines, two definitions of post-acute COVID-19 are given: (1) Ongoing symptomatic COVID-19 for persons who still have symptoms between 4 and 12 wk after the onset of acute symptoms; and (2) Individuals who still have symptoms for more than 12 wk after the onset of acute symptoms. A full blood count, liver and kidney function tests, a C-reactive protein test, and an exercise tolerance test (level of breathlessness, O_2 saturation, and heart rate) are recommended. A chest X-ray also should be advised to all patients by 12 wk after acute infection in cases of persistent respiratory symptoms[3].

Basic mechanisms leading to post-acute COVID-19 include: (1) Virus-related pathophysiologic changes; (2) Immunologic alterations and inflammatory changes in response to the acute infection; and (3) Post-critical illness sequelae. Post-intensive care syndrome is multifactorial and probably due to microvascular ischemia, immobility, and metabolic changes during critical illness. A rehabilitation physician should be well aware of this basic pathophysiology of each aspect of COVID-19 in order to address the rehabilitation need aptly and to implement rehabilitation programs accordingly.

ROLE OF REHABILITATION MEDICINE & INTERNATIONAL CLASSIFICATION OF FUNCTIONING, DISABILITY, AND HEALTH IN COVID-19

Rehabilitation has immense importance during this pandemic considering a few aspects. From the perspectives of type of patient population, there would be different rehabilitation needs for people with COVID-19/post-COVID with no comorbidities/disabilities and those with COVID-19/post-COVID with comorbidities/disabilities. On the other hand, from the perspective of COVID-19 severity, the rehabilitation needs would be different for mild, moderate, and severe/intensive care unit (ICU) admitted patients or in patients with post-intensive care syndrome. Furthermore, at an individual level, a patient may have multiple body-system involvements, in that case, rehabilitation needs would be according to the involvement and impairments. Considering the duration of the disease rehabilitation program would differ, goal setting would change (*e.g.*, acute, subacute, and chronic/post-COVID) accordingly.

At each stage, a basic outline of rehabilitation has to be followed in this sequence: Proper history and physical examination focusing on functional status, a list of problems according to International Classification of Functioning, Disability and Health (ICF) data set (body functions and structure suggesting impairments, activity limitations, participation restriction, and related environmental and personal factors), addressing each problem (management plan: Short- and long-term feasible and realistic goal setting after discussion with the patient, care-giver/partner/family), and trying to achieve each goal, encourage and make support groups to aid in better compliance in the rehabilitation program, to avoid drop-outs, and to strengthen mental health.

Impairments

Multiple system impairments occur like impaired lung function (the viral respiratory syndrome and/or pneumonia, pulmonary fibrosis, pulmonary embolism, damage to respiratory muscles, immobility, and atrophy), physical deconditioning and weakness (due to polyneuromyopathy, inflammatory storm to the muscles, and drugs such as steroids), metabolic changes (*e.g.*, hyperglycemia and malnutrition), immobility and atrophy, impaired communication, impaired swallow (post mechanical ventilation and others), delirium and cognitive impairments, anxiety depression and difficulty in managing activities of daily living (ADLs), pressure injuries, incontinence, polyneuropathy, and other disorders of the peripheral nervous system. Speech-language therapists, physiotherapists, and occupational therapists are needed in such cases.

Rehabilitation starts from acute care setting, then it includes inpatient rehabilitation, outpatient settings, telerehabilitation, and home-based and community-based setting[4].

EVIDENCE-BASED REHABILITATION

We are at the very primary stage to garner evidence for COVID-19. This is the reason why we are continuously modifying and updating guidelines and evidence-based medicine[5]. Studies with stronger evidence on the efficacy of interventions and long-term monitoring are lacking.

Self-management (hospitalized and non-hospitalized)

Objective: The objective is to increase functional independence of patients. Patients with COVID-19 should be educated on self-management regarding breathlessness and gradual activity resumption[6].

Long-COVID: Post-COVID-19 symptoms are seen in > 60% of patients infected by SARS-CoV-2. Fatigue and dyspnoea were the most common post-COVID-19 symptoms, particularly 60 and ≥ 90 d after[7]. Individualized rehabilitation programs from subacute to long-term should be provided according to patient needs. The prescription and provision of rehabilitation programs should be guided by persistent symptoms and functional limitations. Post-COVID-19 impairments like fatigue, weakness, and cognitive impairment, can impact the performance of ADLs. Providing ADL training, considering home modifications (such as grab bars in the shower and toilet, and handrails along stairs), and the provision of an assistive product (such as a mobility aid, shower chair, and over-toilet frame), as needed, are important.

Persons with COVID-19 needs supervised patient-tailored programmes that are flexible enough to adapt for patients. It should be guided by baseline oxygen needs at rest and during exercise.

Persons with physical deconditioning and weakness should start with exercises that help in recovery of daily functioning, start with active range of motion exercises, and when tolerated, proceed with progressive muscle strengthening, typically offered with resistance training.

For individuals having difficulties in memory, concentration, and problem solving, education should be provided, and advice on strategies to reduce stress and anxiety should be given. Cognitive restorative rehabilitation along with cognitive exercises like memory exercises, puzzles, games, and reading and compensation tools like prompts (*e.g.,* lists and notes) and breaking down activities are advised.

For patients with anxiety, depression, and post-traumatic stress disorder, basic mental health and psychosocial support by appropriately trained health or non-health workers should be provided.

For pain, a multidisciplinary approach for pain management is followed according to the biopsychosocial model.

For a successful rehabilitation, a multidisciplinary team approach is essential where a rehabilitation physician (physiatrist) works in collaboration with a group of physicians from multiple specialties (critical care experts, pulmonologists, neurologists, cardiologists, rheumatologists, *etc.*), nursing professionals, pharmacists, occupational therapists, physiotherapists, social workers, mental health experts, community workers, and other health care professionals

SYSTEMIC INVOLVEMENT OF COVID-19 AND THEIR SPECIFIC REHABILITATION APPROACHES

Pulmonary rehabilitation

Pulmonary rehabilitation improves functional capacity and quality of life in persons recovering from SARS-CoV-2 infection[8].

Diffuse alveolar damage, pulmonary vascular microthrombosis, and macrothrombosis, and immunological damage are responsible for pulmonary sequelae and lung fibrosis.

Pulmonary involvement is complicated with pneumonia, pulmonary embolisms, pulmonary fibrosis, and prolonged ventilation induced respiratory muscle weakness.

Based on a level 3 study, it is suggested that a large proportion of patients still present with dyspnoea at 3 wk of hospital discharge and that PaO2/FiO2 ratio and BMI at admission to the Emergency Department are the strongest independent predictors of persistent respiratory impairment and the need for follow-up in these patients[9].

Patients can try relieving breathlessness using a number of positions including standing with back support, forward lean sitting, and forward lean standing.

Because of risk of infection, lung function test using spirometers is not recommended in patients in the first 6-8 wk with COVID-19; later it can be done to test lung function when patients get non-infectious.

Increasing ventilation

Active cycle of breathing techniques (ACBTs) can be used. Sitting up in bed or chair or standing with support positions to improve ventilation can be adopted as it allows increased thoracic expansion.

Airway clearance

Airway clearance is advised when airway obstruction by sputum is suspected, as these are droplet generating techniques.

In most patients, ACBTs may be used for airway clearance. It includes deep breathing with thoracic expansion and then exhaling with a huff. Huffing is forced expiration with an open mouth (vibration frequency < 17 Hz). Huffing helps to move sputum from small airways to larger airways. A sequence of deep breaths (× 3) then 1-2 huffs and a cough can be used to clear sputum.

Bubble PEP (positive expiratory pressure) can also be used and combined with a huffing and cough sequence to help clear sputum.

Breathlessness education

It is important to learn self-management. The following self-management practices may be adopted.

Staying calm: Breathlessness leads to anxiety which may make it worse.

Using positions: There are several positions (high side-lying and forward lean sitting) that can be adopted that offer support to the body to make breathing easier.

Using breathing techniques: Different breathing techniques may be adopted in different situations. Deep breathing and paced breathing techniques are helpful. Pursed lip breathing helps to empty the lungs and can be helpful to remain calm and when doing a moderate level of activity.

Pursed lip breathing: The patient relaxes his/her shoulder and neck muscles, inhales through the nose for two counts (inhale, one, two, do not take deep breath, only normal breath), 'purses' or puckers his/her lips as if he/she is going to whistle, then lastly exhales slowly through pursed lip counting to four (exhale, one, two, three, four).

Square box breathing: The patient closes his/her eyes and inhales *via* the nose (count up to 4), holds the air inside (count up to 4), exhales slowly (count up to 4), and finally holds for count 4.

Patients should start at lower intensities, especially during the first 6 wk following acute illness.

Respiratory muscle training can improve effortless breathing. Inspiratory muscle training (IMT) can be facilitated *via* loading of inspiration, by using a breathing device (threshold IMT or power breathe). Expiratory muscle training is also helpful.

Patients should start with low-intensity exercises (≤ 3 METs or equivalent or Borg dyspnea score ≤ 3; duration: 10-15 min for first 3-4 sessions; frequency: 1-2 times/d, 3-4 times/wk) and increase slowly by 30 s to 1 min each time. Over time progression of exercises can be increased up to a Borg score of 4-5 and duration to 30-45 min for 2-3 sessions. Frequency and intensity should be individualized. Pulse oximeter is used to monitor oxygen saturation. Stop physical activities or exercises when a patient's saturation drops more than 5%-10% during exercise. Warm-up and cool-down exercises are recommended. Exercises in the home environment along with maintaining an exercise logbook are recommended[10].

At 12 wk post-discharge, all COVID-19 patients are recommended to be assessed clinically along with an evaluation with chest X-ray, for rehabilitation needs, pulmonary function tests, 6-min walking tests, sputum sampling, and echocardiogram according to clinical judgment. In cases of persistent dyspnea, high-resolution computed tomography of the chest at 6 and 12 mo is also recommended.

Cardiac rehabilitation

According to initial assessment, cardiology consultation should be taken, and further investigations are advised like blood panel, ECG, 24 h ECG, echocardiogram, cardiopulmonary exercise testing, and/or cardiac magnetic resonance imaging.

A 3-6 mo period of complete rest, based on clinical severity and duration of illness, left ventricular function at onset, and extent of inflammation on CMR, is required for patients returning to high-level sport or physically demanding occupation following myocarditis. Training and sport may resume following myocarditis, if left ventricular systolic function and serum biomarkers of myocardial injury are normal and if relevant arrhythmias are ruled out on 24 h ECG monitoring and exercise testing. Periodic assessment is needed in the first 2 years[11].

Abstinence from competitive sports or aerobic activity for 3-6 mo is recommended for competitive athletes with post-COVID cardiovascular complications and it should be until resolution of myocardial inflammation revealed by cardiac magnetic resonance imaging or troponin normalization. Serial clinical and imaging evaluation at 4-12 wk with electrocardiogram and echocardiogram may be done in those with cardiovascular complications.

Rheumatological rehabilitation (arthralgia, arthritis, and myalgia)

Early COVID-19 studies have indicated that over a quarter of mechanically ventilated patients continue to experience ICU acquired weakness at discharge from hospital[12], while half of all hospitalized patients continued to experience fatigue at 60 d post onset[13]. Physical difficulties were reported, including strength, balance, pain, exercise tolerance, and fatigue. Medical Research Council score,

handgrip test, Berg balance score, and time up and go test are important assessment measures. SPO2 during exercises and exercise tolerance test (step test or sit to stand test) should be done. Early mobilization (should begin in ICU and critical care setting if tolerable and feasible; bed mobility, bed exercises, *etc.*), education on fatigue and breathlessness, and functional mobility are to be focused. Energy conservation techniques should be considered, such as simplifying tasks, spacing activities throughout the day, and resting before and after activities. The patient should resume his/her everyday activities and exercise slowly, gradually increasing time and exertion levels, and avoid strengthening exercises until myalgia resolves. For immobile patients with profound weakness, the daily use of neuromuscular electrical stimulation is considered to address inactivity-induced atrophies in lower-limb muscles. Biceps curl, knee strengthening, squats, heel raisers, wall push up, sit-to-stand, *etc.* are strengthening exercises. The patient should start the exercise in low-moderate intensity and then gradually increase accordingly. In the initial 6 wk after discharge or illness, it is recommended to keep shortness of breath or fatigue below 4/10 on the Borg scale. Clinical signs of desaturation should be monitored using a pulse oximeter when possible. Exercise must be individually prescribed with specifying training parameters regarding frequency, intensity, duration, and type and exercises must be done in a safe environment. Walking, jogging, cycling, step-ups, and marching on the spot may be undertaken if no contraindications exist.

Post-mechanical ventilation patients or those in tracheostomy may develop speech or voice issues. Assessment of any changes in voice quality and articulation problems is needed. Even in intubated patients if conscious, means of communication like notepad, communication board, *etc.* should be provided. The use of communication boards, communication devices, computers, and smartphone apps is encouraged to augment communication. Using voice is practiced gently through singing, reading aloud, and conversation. The patient should stay hydrated and sip water throughout the day. Optimal oral hygiene is practiced to minimize the risk of infection and maximize healing of the vocal structures. Patients with a tracheostomy may be fitted with a speech valve, which enables speaking without the use of the vocal folds, a trained physician is needed to manage these things and associated caregiver education.

Post-COVID patients may also develop steroid-induced myopathy.

Neurorehabilitation like COVID-induced spinal cord injury, post-COVID stroke, and neuropathy

Hemorrhagic stroke, hypoxic-anoxic damage, posterior reversible encephalopathy syndrome, and acute disseminated myelitis are reported in post-COVID cases.

Stroke patients developing COVID-19 have a worse prognosis, with an over nine-fold increase in mortality and a higher probability of requiring rehabilitation[14].

Regarding the natural history of COVID-19, the case series concerning four severe COVID-19 patients with HO in the hips and shoulders after 30-40 d of hospital admission suggests that the global inflammation associated to COVID-19 might play a role in the pathophysiology of HO, and enhances the need for early monitoring of joint mobility and careful mobilization of patients in the acute phase.

Cognitive domains that may be affected after severe or critical illness with COVID-19 include (but are not limited to) basic functions such as attention, concentration, and memory, higher-order functions such as problem solving, decision making, and judgement, and language such as verbal and semantic memory. Nervous system involvement is due to hypoxic encephalopathy, neuroinflammation, direct viral invasion, and sepsis associated encephalopathy.

Cognitive activities: Puzzles, word and number games, memory exercises, and reading may help improve cognitive function. COVID-19 patients with cognitive function impairment should start with activities that are challenging but achievable and increase the difficulty as able. This is important for keeping the patient motivated. These patients should participate in daily activities. Compensation strategies (prompts: Lists, notes, and alerts, such as phone alarms, can be useful for patients with impaired memory, breaking down activities into individual steps can help prevent the patient from feeling overwhelmed, and relaxation exercises, including meditation, can help alleviate the stress that may be caused by and exacerbate cognitive impairment) should be followed.

Olfactory Training and Visual Stimulation Assisted by a web application for patients with persistent olfactory dysfunction after COVID-19 showed significant improvement after 28 d[15].

Olfactory training like repeated and deliberate sniffing for 20 s each of a set of odorants (commonly lemon, rose, cloves, and eucalyptus) should be conducted at least two times a day for at least 3 mo. Studies have shown improvement in olfaction in postinfectious cases after olfactory training[16]. Intranasal vitamin A and systemic omega-3 may serve as adjuvant therapies[17].

Gastrointestinal system involvement

Diarrhoea, vomiting, and nausea are common in COVID. In cases of persistent gastrointestinal issues, nutritional assessment and micronutrient blood panel may be warranted. Decreased appetite and weight loss sometimes may occur, which also needs attention. A liver function test should be advised as hepatic dysfunction is common in severe COVID-19 cases. COVID-19 has the potential to alter gut microbiome.

Renal system involvement

Acute kidney injury tends to occur in 5% of all cases and 20%-31% of critical cases. Acute tubular necrosis is a common finding along with COVID-19 associated nephropathy. A kidney function test is advised as acute kidney injury has been encountered in many severe COVID-19 cases. Renal involvement is due to sepsis, septic shock, immunoinflammatory reactions, and drug-induced or post-steroid therapy. Patients with renal dysfunction may need a changed or individualized exercise regime and hydration advice.

Haematological system involvement

Lymphopenia, anemia, and leucopenia are common and at times thrombocytopenia can occur. Patients with COVID-19 are susceptible to pulmonary embolism and venous thromboembolism. Before starting any exercises regime, a complete hemogram should be done, and in clinically suspicious cases of thromboembolism, specific investigations are warranted.

Endocrine system involvement

Due to COVID-19 itself or after steroid therapy, hyperglycemia may occur. Post COVID-19 diabetic ketoacidosis and subacute thyroiditis with clinical thyrotoxicosis have been reported. Periodic assessment is needed in such cases.

Other system involvement

Swallowing challenges associated with COVID-19 may result from intubation induced damage in the mucous membrane of the oral cavity, nasal cavities, and/or pharynx, weakening of the swallowing mechanism, diminished swallowing reflexes and muscle tone associated with inflammation, polyneuropathy, and side-effects of medications, cognitive impairment affecting safe swallowing, ventilation induced changes in viscosity of saliva, mouth breathing, medication, or dehydration.

Rehabilitation exercises addressing each of the cardiopulmonary, neurological, vestibular, musculo-skeletal, and mental/cognitive systems are recommended in a phased manner (beginning, building, and being phase). In the beginning phase, deep breathing (3 min), eye nodding, bed rolling, head nods, rocking on knees, *etc.* (3 min) can be tried. Subsequently, the patients can engage in crossbody patterns such as crawling, seating, or standing cross-crawl touches, marching, or walking (1 min). These can be followed by strength building by 'yawn to smile', biceps curls, shoulder press, heel raise, wall push-up, and mini-squats (1-3 min). Endurance building by 5-45 min walk can be done in a gradually increasing manner in all phases[18].

DISABILITY INCLUSIVE

Since the beginning of 2022, India has been facing the third wave of this pandemic. Considering the huge population and people with low socioeconomic status, rehabilitation of COVID-19 in the Indian setting can be an ideal example of other developing countries. In the Indian scenario, people with different abilities face different sorts of barriers during the pandemic. Moreover, globally people with disabilities (15% of the global population) have been affected negatively by the COVID-19 pandemic. The risk of death from COVID-19 (January 24-November 30, 2020) in England was (men: 3.1 times greater; female: 3.5 times greater) greater in people with disabilities than in those without disabilities [19]. As usual, ICU patients had more disabilities than ward patients [20]. A person with long COVID-19 will have a disability if his/her condition or any of its symptoms is causing physical or mental impairment that hinders one or more major life activities[21]. People with disabilities are susceptible to COVID-19. In India, Rights of Persons with Disabilities Act, 2016 (Section 8) guarantees the equal protection and safety for people with disabilities in such situations.

SPECIAL CLINICS AND COMMUNITY-BASED REHABILITATION

In the Indian setting, post-COVID rehabilitation clinics (adult and pediatric) are the key need currently like in the United States[22]. Community-based rehabilitation would be effective in the Indian setting to cater rehabilitation services. Falvey *et al*[23] showed how community-based therapists can help during pandemics. During the pandemic, the community health workers contribute to the COVID-19 response; it includes screening, referrals, arranging support for home care, staffing community-based isolation centres, and being involved in surveillance, contact tracing, service delivery to people with disabilities, home visit, outreach activities, and campaigns[24].

CONCLUSION

"Rehabilitation is an essential health service and crucial for achieving universal health coverage" (Rehabilitation 2030 initiative). Needless to say, globally rehabilitation for people with COVID-19 and post-COVID-19 syndrome is the key unmet need. We would like to conclude this chapter with some recent advances which can further the rehabilitation process, especially artificial intelligence (AI) and telerehabilitation. A patient-centric individualized AI system for home-based rehabilitation is beneficial [25,26]. AI can be useful to make early detection of long-COVID symptoms. Hassanien *et al*[27] showed machine learning to better understand and predict the reaction of patients to the disease and the possibilities that they may have for recovery. Furthermore, the TERECO trial showed the effectiveness of telerehabilitation in COVID-19 survivors[28]. Werneke *et al*[29] showed the importance of telerehabilitation during pandemic times in outpatient rehabilitation settings. Telemonitoring is generally recommended 1-4 times in the first-month post-discharge. Follow-up recommendation is based on the Barthel Index score: level 1 (0-39, dependent, weekly telemonitoring), level 2 (40-79, partially dependent, biweekly telemonitoring), and level 3 (80-100, independent, monthly telemonitoring). In this ultra-modern era with cutting-edge technology, at the end of the chapter we would like to emphasize that prevention against the development of disease or disability is far easier and more economical than the disease itself. All you need to do is to practice basic personal hygiene, a healthy active lifestyle, and comprehensive rehabilitation to prevent disease, disability, and death. Finally, rehabilitation need identification is an important step to evaluate long COVID-19 patients so that we can recognize them early to prevent disability[30].

Take-home message

What are the issues that individuals need to be supported in rehabilitation: Rehabilitation needs should be identified according to the ICF.

Currently, studies are going on to find out rehabilitation needs in these patients. However, physicians have to identify needs by focusing each body system and emphasizing on patient's functional aspects.

Early rehabilitation intervention even when patient is in ICU is of utmost importance apart from post-discharge rehabilitation.

How should these requirements be met: Proper rehabilitation facilities and infrastructures as mentioned in Rehabilitation Initiative 2030 (World Health Organization) should be provided.

A multidisciplinary post-COVID rehabilitation clinic at tertiary hospitals, as well as outdoor and indoor COVID-19 rehabilitation facility, is required.

Future research: Observational studies are needed to find out post-COVID rehabilitation need in able-bodied individuals and also in differently-abled individuals.

Future trials are required to find out the effectiveness of specific interventions to improve functional status of people with long COVID.

FOOTNOTES

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MINIREVIEWS

Gut microbiota interactions with anti-diabetic medications and pathogenesis of type 2 diabetes mellitus

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Abstract

Microorganisms including bacteria, viruses, protozoa, and fungi living in the gastrointestinal tract are collectively known as the gut microbiota. Dysbiosis is the imbalance in microbial composition on or inside the body relative to healthy state. Altered Firmicutes to Bacteroidetes ratio and decreased abundance of Akkermansia muciniphila are the predominant gut dysbiosis associated with the pathogenesis of type 2 diabetes mellitus (T2DM) and metabolic syndrome. Pathophysiological mechanisms linking gut dysbiosis, and metabolic diseases and their complications include altered metabolism of short-chain fatty acids and bile acids, interaction with gut hormones, increased gut microbial metabolite trimethylamine-N-oxide, bacterial translocation/Leaky gut syndrome, and

endotoxin production such as lipopolysaccharides. The association between the gut microbiota and glycemic agents, however, is much less understood and is the growing focus of research and conversation. Recent studies suggest that the gut microbiota and anti-diabetic medications are interdependent on each other, meaning that while anti-diabetic medications alter the gut microbiota, the gut microbiota also alters the efficacy of anti-diabetic medications. With increasing evidence regarding the significance of gut microbiota, it is imperative to review the role of gut microbiota in the pathogenesis of T2DM. This review also discusses the interaction between gut microbiota and the various medications used in the treatment of T2DM.

Key Words: Metabolic disease; Gut microbiota; Cardiovascular disease; Short chain fatty acid; Dysbiosis; Trimethylamine-N-oxide

Core Tip: Gut microbiota influence the pathogenesis of type 2 diabetes mellitus (T2DM) and metabolic syndrome through multiple mechanisms. The role of dysbiosis and various pathophysiological mechanisms such as altered metabolism of short-chain fatty acids, interaction with gut hormones, increased gut microbial metabolite trimethylamine-N-oxide and bacterial translocation in the pathogenesis of T2DM and cardio-metabolic diseases have been extensively studied. With increasing evidence regarding the significance of gut microbiota, it is imperative to review the role of gut microbiota in the pathogenesis of T2DM. This review also discusses the interaction between gut microbiota and the various medications used in the treatment of T2DM.

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INTRODUCTION

Diabetes mellitus is a common chronic endocrine disorder with an estimated global burden of 537 million adults worldwide and projections indicate that the number of diabetic patients worldwide, will reach 700 million by 2045[1]. Diabetes is characterized by raised blood glucose levels arising as a consequence of decreased insulin production, resistance to insulin action or both. Traditional risk factors of developing type 2 diabetes mellitus (T2DM) include family history of diabetes, advancing age, obesity, sedentary lifestyle and poor-quality diet. Over the last decade, multiple studies have indicated a possible causal role of alterations in gut microbiota with development of T2DM[2-4]. Various studies are exhaustively exploring the role of gut microbiota as a biomarker for T2DM and a possible therapeutic intervention to treat T2DM[5-9].

Microorganisms including bacteria, viruses, protozoa, and fungi living in the gastrointestinal tract (GI) are collectively known as the gut microbiota. Over 100 trillion microbes live in our gut, particularly in the large intestine[10]. Taxonomically bacteria are classified as species, genus, family, order and phylum. Human gut microbiota is primarily composed of 5 phyla namely Bacteroidetes, Firmicutes, Actinobacteria, Proteobacteria and Cerrucomicrobia[11]. Firmicutes (*i.e., Bacillus* spp.) and Bacteroidetes (*i.e., Bacteroides* spp.) account for 90% of the gut microbiota community[11]. Their primary physiological roles in humans include protection against pathogens, producing vitamin B and K as well as bile acids, and a very pivotal role in host metabolism and immune modulation[12,13]. The composition of gut microbiota is regulated by factors such as genes, diet, geographical factors and medication use[13-15].

The development of PCR-based techniques has shown the way for the characterization and quantification of bacterial composition *via* sequencing of bacterial genes in human fecal sample. This has enabled scientists and physicians around the world to understand the role of gut microbiota and its interplay with multiple pathological conditions. In this review article we discuss the role of gut microbiota in the development of T2DM and therapeutic action of anti-diabetic drugs.

GUT DYSBIOSIS AND ITS ROLE IN PATHOPHYSIOLOGY OF T2DM

Dysbiosis is the imbalance in microbial composition on or inside the body relative to healthy state. Dysbiosis is associated with several autoimmune and inflammatory pathological conditions including allergies, central nervous system disorders, cancers, metabolic syndrome, diabetes mellitus, polycystic ovarian syndrome and cardiovascular disease[16,17]. Altered Firmicutes to Bacteroidetes ratio and decreased abundance of Akkermansia muciniphila are the predominant gut dysbiosis associated with the pathogenesis of T2DM and metabolic syndrome (Figure 1).

The ratio of Firmicutes to Bacteroidetes is increased in obese patients and during consumption of high calorie diets[2,18-21]. The altered ratio of these two major phyla leads to impaired glucose metabolism and an increase in obesity[22]. Decreasing the amount of Firmicutes and increasing the proportion Bacteroidetes leads to weight loss and reduced inflammation. T2DM is also associated with dysbiosis and have shown decreased abundance of Bacteroides[3,19] and propionate-producing bacteria such as Akkermansia muciniphila[3,4,19,23].

Akkermansia muciniphila is an anaerobic gram-negative bacteria that has shown to affect glucose metabolism, lipid metabolism and promote intestinal immunity[24]. Akkermansia muciniphilais found in abundant quantity in gut mucosa which utilizes mucin as its energy source and produces mucin degrading enzymes[25] thereby playing a crucial role in gut barrier function. Goblet cells in the gastrointestinal tract produce a thick layer of mucus which serves as a protective barrier against pathogens. The breakdown of intestinal mucosal barrier seen in patients with diabetes can be altered by this microbiota *via* its mucus secreting action. Akkermansia-induced extracellular vesicles may help regulate gut permeability[24]. Lipopolysaccharide (LPS) is an endotoxin derived from gram negative bacteria and plays a role in increasing gut permeability and thereby promoting the inflammatory process[26]. LPS level in blood has been shown to be elevated in high fat diet (HFD) mice and mice with diabetes, which decreases following the administration of Akkermanisa[26].

Akkermansia muciniphila also upregulates the endogenous production of GLP1 thereby increasing postprandial insulin secretion[27]. In humans, levels of Akkermansia muciniphila were found to be decreased in diabetes mellitus and obesity whereas the levels of Akkermansia muciniphila increased with treatment with anti-diabetic drugs and weight loss bariatric surgery[28-30]. Akkermansia muciniphila, in fact, is considered a next generation probiotic as there is large body of evidence linking decreased abundance of Akkermansia muciniphila with development of diabetes and obesity[31,32].

Research over last couple of decades have elucidated several pathophysiological mechanisms by which gut microbiota influences the pathogenesis of T2DM and metabolic syndrome. Pathophysiological mechanisms linking gut dysbiosis, and metabolic diseases and their complications include altered metabolism of short-chain fatty acids (SCFAs), interaction with gut hormones, increased gut microbial metabolite trimethylamine-N-oxide (TMAO), bacterial translocation/Leaky gut syndrome, and endotoxin production such as LPS.

Complex sugars are metabolized into SCFA in the colon by gut microbiota, which are known to reduce inflammation and improve glucose homeostasis (Figure 2). These SCFA specifically butyrate, acetate and propionate modulate the insulin release and hunger by increasing endogenous Glucagon like peptide1 (GLP1) and Protein YY (PYY) secretion[33]. The mechanism of action of this process is based on the interaction between SCFAs and G-protein-coupled free fatty acid receptors GPR41 and GPR43. SCFAs directly bind to receptor GPR41 and GPR43 to mediate release of GLP1 and PYY from intestinal L cells[34].

GLP-1 secreted by intestinal L cells increases the secretion of glucose-induced insulin from pancreatic β-cells, decreases the secretion of glucagon and delays gastric emptying[35]. GLP1 receptor analogs are an established method of treating T2DM nowadays. Pancreatic islet-derived PYY plays an important role in controlling glucose homeostasis through the modulation of β-cell mass as well as by increasing insulin secretion[36].

Researchers and clinicians have been cautiously optimistic that gut microbiota modulation has the potential to be a novel therapeutic target for T2DM treatment. It has been noted that ingestion of fermentable dietary fibers increased SCFA concentration, whereas the high-fat diet reduced formation of SCFAs[33]. Chambers *et al*[37] showed that SCFA propionate supplementation significantly reduced weight gain in overweight adults by increasing their postprandial secretion of GLP-1 and PYY. A previous study also showed that per rectal administration of SCFA significantly raised the plasma GLP1 and PYY concentrations, thereby further suggesting the beneficial effects of gut microbiota modulation in patients with T2DM[38,39].

Dysbiosis also leads to increased inflammation and atherogenesis through the gut microbial metabolites, TMAO and its precursors. Choline is an important nutrient which is found in foods such as red meat, fish, poultry and eggs. Gut microbiota metabolizes choline into Trimethylamine (TMA) which is further transported to liver *via* portal venous circulation where TMA is oxidized into TMAO [39]. Plasma levels of TMAO are positively associated with degree of atherosclerosis in a dose dependent manner[40]. Several studies have implicated TMAO levels as a risk factor for cardiovascular disease and mortality[17,41]. However, recent studies have also shown association of higher TMAO levels with diabetes, gestational diabetes and obesity[42-44].

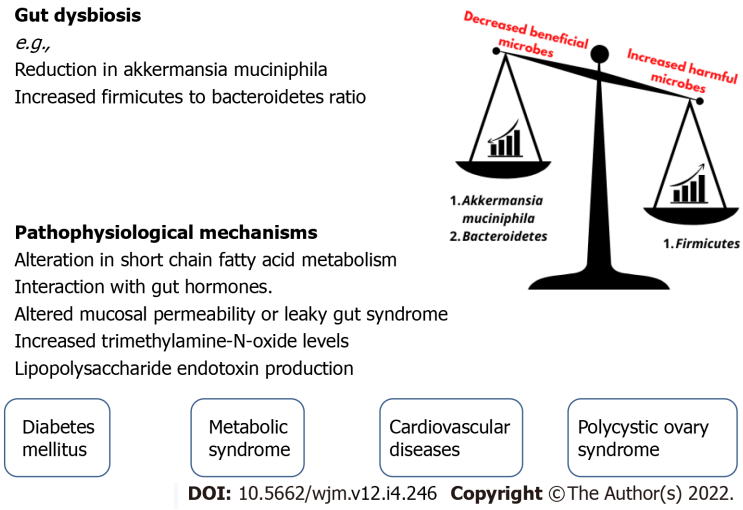

Figure 1 Gut dysbiosis and its role in pathophysiology of type 2 diabetes mellitus and cardio-metabolic diseases.

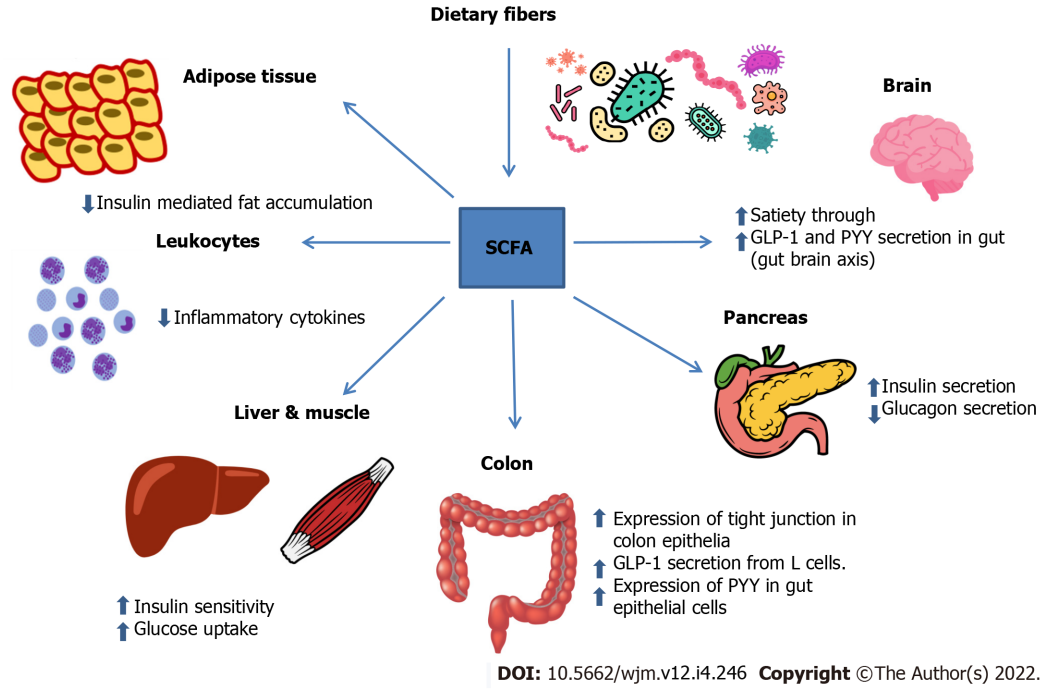

Figure 2 Role of gut microbiota and short-chain fatty acids in the pathophysiology of diabetes mellitus. SCFA: Short-chain fatty acids; GLP-1: Glucagon-like peptide-1; PYY: Peptide YY.

Dysbiosis also leads to disruption of gut epithelial barrier leading to excessive absorption of gut microbiota produced LPS. LPS is a strong endotoxin present in the outer membrane of gram-negative bacteria that can trigger an immune response associated with inflammation. Continuous absorption of LPS evokes a chronic inflammatory response and increased LPS levels are associated with diabetes and insulin resistance[45].

IMPACT OF GUT MICROBIOTA ON ANTI-DIABETIC DRUGS

The composition of an individual's gut flora is known to have an influence on metabolism and glucose homeostasis. The association between the gut microbiota and glycemic agents, however, is much less understood and is the growing focus of research and conversation. Recent studies suggest that the gut microbiota and anti-diabetic medications are interdependent on each other, meaning that while diabetic medications alter the gut microbiota, the gut microbiota also alters the efficacy of diabetic medications. Below, the results of various studies surrounding the relationship between various glycemic

medications and the gut microbiota will be reviewed.

Since the composition of gut flora is known to influence glucose homeostasis, it is vital to understand the impact of anti-diabetic medications on the gut microbiota to fully comprehend their mechanism of action (Table 1).

METFORMIN

Metformin has the strongest data regarding impact of gut microbiota on its therapeutic effects among all anti-diabetic medications. Metformin use has shown to promote the growth of various SCFA-producing healthy bacteria[5,30]. In a double-blinded randomized control trial, Wu Hao and colleagues included treatment-naive patients with T2DM to receive either 4 months (mo) of metformin or placebo[5]. Treatment with metformin for 4 mo, compared to placebo, showed an increment in the following SCFA producing bacteria such as Blautia, Bacteroides, Butyricoccus, Bifidobacterium, Prevotella, Megasphaera and Butyrivibrio, and increase in fecal concentration of lactate as well as a trend towards an increase in the fecal concentration of succinate. In the same study, metformin treatment for 2 mo, led to an increase in the microbial genera such as Proteobacteria and Firmicutes[5].

Metformin use is also associated with an increase in the mucin degrading microbiota, Akkermansia muciniphila[29,30,46]. As described in detailed earlier in this article, Akkermansia muciniphila affects glucose metabolism through regulating gut permeability, decreasing LPS and increasing postprandial insulin secretion through interaction with GLP-1[24,26,27]. A study involving community-dwelling Colombian adults showed that participants with diabetes taking metformin not only had high abundance of gut microbiota known for production of SCFAs (Butyrivibrio, Bifidobacterium bifidum, Megasphaera, and an operational taxonomic unit of Prevotella) but also had higher relative abundance of Akkermansia muciniphila, in comparison to participants without diabetes[30].

Studies in mice have shown an association between metformin treatment and an increase in the abundance of Akkermansia muciniphila in the gut flora of mice that were placed on a high fat diets[29,46]. Metformin use has also shown to have a positive effect on the gut microbiota in mice on a normal diet[46]. An abundance of microbes belonging to families such as Rikenellaceae, Ruminococcaceae, and Verrucomicrobiaceae, and an abundance of microbes belonging to species such as Alistipes, Akkermansia, and Clostridium were noted in the experimental mice with normal diet plus metformin treatment than in the control group[46,47].

There is also a suggestion that the cardiovascular protective effects of metformin may be mediated by gut microbiota. Metformin treatment in db/db mice with T2DM resulted in a twofold reduction in the concentration of TMAO and also decreased bacterial production rate of TMAO precursors[44]. Authors postulated that reduction in TMAO levels with metformin use may contribute to cardiovascular benefits of the drug.

Based on the large body of evidence summarized above, it is safe to say that metformin has consistently shown a beneficial effect towards improving the gut health and cardiovascular health.

GLP-1 RECEPTOR AGONISTS

GLP-1 is an incretin hormone secreted by the intestinal endocrine cells known as the L cells, in response to food ingestion and causes glucose-mediated insulin secretion from the beta cells of the pancreas, concomitant suppression of glucagon from the alpha cells of the pancreas and a decrease in gastric emptying[6]. GLP-1 receptor agonists (GLP-1 RAs) use in patients with T2DM not only results in improved glycemic control but has also shown to promote weight loss, favorable effects on blood pressure and cholesterol, and decreased cardiovascular morbidity and mortality[48]. Therefore, there has been a great interest in the research community to understand underlying mechanisms resulting in GLP-1 RAs therapeutic benefits.

Limited data available on impact of GLP-1 RAs on gut microbiota suggests that clinical benefits of GLP-1 RAs may be mediated by modulation of gut microbiota. Current data suggests that GLP-1 expression could be stimulated by the binding of SCFAs, which are produced by the degradation of carbohydrates by the gut bacteria, to the free fatty acid receptor 2[19]. GLP-1 RAs have shown to be associated with decreased dysbiosis particularly increase in Bacteroidetes to Firmicutes ratio, decrease in obesity-related and an increase in lean-related microbiota phenotypes, and an increase in abundance of Akkermansia[49-52].

Gut microbiota in obese people lack microbial diversity and specifically there is a decline in the Bacteroidetes population along with an abundance in the Firmicutes population resulting in decreased Bacteroidetes to Firmicutes ratio[46]. This was shown in a recent study which compared the fecal microbiota of European children (EU) and the children from Burkina Faso (BF), a rural African village where the diet is rich in fiber. There was a significant abundance in bacteroidetes and a reduction in Firmicutes in the BF children in comparison to the EU children. In one study, several mouse models that were subjected to a probiotic known as VSL#3, led to a suppres-sion of weight gain and insulin

Table 1 Impact of anti-diabetic medications on the gut microbiota

Drug	Changes in microbiota
Metformin	Increase in SCFA producing bacteria[5,30], Akkermansia muciniphila[29,30,46], Firmicutes[5] and Proteobacteria[5]; Increased fecal concentrations of lactate and succinate[5]; Decreased concentration of TMAO and its precursor metabolites[44]
Liraglutide	Increase in Bacteroidetes to Firmicutes ratio[49] and Akkermansia[50]; Increase in lean related phenotypes (Blautia and Coprococcus) [49]; Decrease in Obese related phenotypes (Romboutsia, Ruminiclostridium and Erysipelotrichaceae)[49]
Dulaglutide	Increase in Bacteroidetes to Firmicutes ratio[51]
Sitagliptin	Increase in Bacteroidetes to Firmicutes ratio[7]; Increase in SCFAs and other organic acids like succinate[54]
Saxagliptin	No change in Bacteroidetes to Firmicutes ratio[49]; Obesity related phylotype= Decrease in only one genus Candidatus Arthromitus[49]; Lean related phenotype= Increase in the family Lactobacillaceae but Decrease in genus Balutia and Coprococcus[49]
Vildagliptin	Increase in lactobacillus species and propionate[8]; Decrease in Oscillibacter species[8]
Linagliptin	Increase in Bacteroidetes and decrease in Protobacteria species[8]
Empagliflozin	Increase in Bacteroidetes to Firmicutes ratio[51]
Dapagliflozin	Increase in Bacteroidetes to Firmicutes ratio[9]; Increased Oscillospira and Akkermansia muciniphila species[9]
Canagliflozin	Increase in Bacteroidetes to Firmicutes ratio[57]; Increase in Olsenella[57], Alistipes[57], Alloprevotella[57] and Lactobacillus species[58]; Decrease in Helicobacter and Mucispirillum species[57]
PPARγ agonists	Firmicutes and Fusobacteria stimulate PPAR gamma activity[63]
Acarbose	Increase in Lactobacillus and Dialister genera[66]; Decrease in Butyricicoccus, Phascolarctobacterium, and Ruminococcus genera[66]; Increase in the ratio between primary bile acids and secondary bile acids[70]
Sulfonylureas	Glicazide have not shown any significant differences on gut microbiome in diabetic patients after 12 wk of intervention[68]

SCFA: Short chain fatty acid; TMAO: Trimethylamine N-oxide.

resistance by altering the gut microbiota. VSL#3 specifically decreased the quantity of Firmicutes and increased the quantity of Bacteriodetes, a change which was associated with an increase in Butyrate production which in turn increased the secretion of GLP-1 from the intestinal L-cells[53].

The above beneficial alteration of gut microbiota is also seen with liraglutide administration. A study showed an increase in the Bacteroidetes to Firmicutes ratio leading to weight loss regardless of the glycemic status in mice with liraglutide use[49]. This study also showed a decrease in obesity-related phylotypes such as Romboutsia, Ruminiclostridium and Erysipelotrichaceae, and an increase in lean-related phylotypes such as Blautia and Coprococcus in mice treated with liraglutide[49].

Like metformin, liraglutide has also been associated with an increased in the presence of Akkermansia[50]. In fact, one study comparing the effect of metformin *vs* liraglutide on the gut microbiota in patients with T2DM, showed higher concentrations of Akkermansia in subjects receiving Liraglutide compared to metformin[50].

Dulaglutide is another GLP-1 agonist used in the treatment of T2DM. Currently, there is limited data on the impact of dulaglutide use on gut microbiota. However, one recent study showed a decrease in the pro-inflammatory pathways and microbiota dysbiosis, specifically an increase in the Bacteroidetes to Firmicutes ratio, in non-diabetic mice with non-alcoholic steatohepatitis after treatment with either dulaglutide or empagliflozin, or both (NASH)[51].

To date, there are no studies looking at the effect of Semaglutide and Exenatide on gut microbiota.

Given the literature showing favorable modulation of gut microbiota with GLP-1 agonists use and our current understanding of role of gut microbiota in the pathophysiology of T2DM and metabolic syndrome, it is not unreasonable to hypothesize that GLP-1 agonists may exert their therapeutic benefits in patients with T2DM through alteration of gut microbiota. However, further studies are needed, particularly in human subjects, to validate these findings and improve our understanding of this topic.

DIPEPTIDYL PEPTIDASE 4 (DPP-4) INHIBITORS

Sitagliptin has shown to exert a beneficial effect on the gut microbiota. Liao X *et al*[7] analyzed the effects of Sitagliptin and acarbose on the gut microbiota in mice on high fat diet. The alteration in 24 genera induced by high fat diet were protected by sitagliptin. A total of 75% of genera increased by sitagliptin belonged to Bacteroidetes and 87.5% of genera decreased by sitagliptin belonged to Firmicutes thus resulting in increased Bacteroidetes to Firmicutes ratio[7]. This study also performed metabolomics analysis which demonstrated that DPP-4 inhibitors changed the pattern of metabolites

linked to carbohydrate, amino acid and nucleic acid metabolism. There was a trend towards an increase in SCFAs and other organic acids like succinate, both of which are already known to improve glucose tolerance and insulin sensitivity[54].

Saxagliptin was compared with liraglutide in one study to evaluate their individual effects on gut microbiota in mice[49]. Although liraglutide showed a prominent effect on the microbial diversity as mentioned in the subsection of GLP-1 RAs above, saxagliptin did not show any significant shift of the microbial composition. Among the liraglutide treated group, there was a significant reduction in all the obesity-related phylotypes whereas only one phylotype (genus Candidatus Arthromitus) decreased with saxagliptin. With regards to the lean-related phylotypes, although both medications led to a similar enrichment in the family Lactobacillaceae and the genera Lactobacillus and Turicibacter, only liraglutide caused an enrichment of the genus Balutia and the genus Coprococcus and these two were decreased in the saxagliptin group. There were also no significant changes in the phyla Firmicutes and Bacteroidetes [49].

Vildagliptin has also shown to impact the composition of the gut microbiota and its metabolic activity. In one study, male mice placed on a western diet plus vildagliptin not only showed a significant reduction in DPP-4 activity in the feces but also a reduction in Oscillibacter spp, and an increase in lactobacillus spp and propionate[8].

Linagliptin was studied along with a sulfonylurea in diabetic patients already on treatment, to evaluate their impact on human gut flora. Following 4 wk of treatment with either medication in a total of 5 patients with MODY and 19 patients with T2DM, there was no significant changes in the gut microbiota[55]. Another study evaluated the changes caused by linagliptin and a purified Peroxisome proliferator-activated receptor- alpha (PPAR-alpha) agonist (WY14643) on various GI parameters such as gut microbial composition, intestinal barrier integrity, endotoxemia, and hepatic energy metabolism in mice on a high-fructose fed diet (HFRU). The HFRU group showed glucose intolerance, endotoxemia, dysbiosis with increased Proteobacteria and a parallel decrease in Bacteroidetes, significant liver inflammation and steatosis. The Linagliptin and PPAR-alpha agonist group in comparison to the control group, had a positive impact on all the above pathological changes which included restoration in the abundance of Bacteroidetes, a significant decrease in Protobacteria species, protection of the intestinal ultrastructural damage, restoration of the intestinal permeability and improvement in hepatic steatosis *via* beta oxidation[56].

Based on the current evidence summarized above, not all DPP4 inhibitors seem to have a positive impact on gut microbiota. The limited studies involving Linagliptin may have shown a benefit due its combination with a PPAR- alpha agonist, which is known to play a role in intestinal cell metabolism, differentiation, and inflammation. Although, the studies involving Sitagliptin and Vildagliptin have shown a benefit, they were conducted in mice. Future studies in humans are awaited to see if the results from the current studies can be replicated or not.

SGLT-2 INHIBITORS

Empagliflozin has been studied along with liraglutide in non-diabetic mice with NASH, to examine their effects individually or in combination, on inflammatory pathways, hepatic steatosis and microbiome dysbiosis[51]. After placing the mice on a high-fat-high-fructose diet with cholesterol surplus for 12 wk, they were randomized to receive either empagliflozin or dulaglutide or both. Neither medication showed an effect on hepatic steatosis in the non-diabetic mice. Only dulaglutide, as a single agent and in combination with empagliflozin showed a beneficial effect on weight loss, glucose homeostasis, anti-inflammatory, and anti-fibrotic pathways. There was no beneficial effects seen with empagliflozin alone. Nevertheless, both medications, alone and in combination, showed a beneficial effect on gut microbiota with an increase of Bacteroidetes and a decrease of Firmicutis[51].

Dapagliflozin has also shown to mildly alter the gut microbiota composition in mice with T2DM. Eight wk after being randomized to receive either a standard diet *vs* a standard diet with dapagliflozin, male diabetic mice in the dapagliflozin group increased the Bacteroidetes to Firmicutes ratio, and increased Oscillospira and Akkermansia muciniphila. It also significantly lowered arterial stiffness and caused a reduction in hyperglycemia and inflammatory markers[9].

Canagliflozin was studied in male mice after inducing T2DM in them by giving a HFD for 24 wk[57]. Various cardio-metabolic parameters and changes in the colonic gut microbiota were assessed. Following treatment with canagliflozin, there were reductions in the lipid profile which was associated with lowering the index for atherogenesis and arteriosclerosis, a reduction in the vascular basement membrane thickness and markers of oxidative stress. It also altered the ratio of Firmicutes to Bacteroidetes from 230% to 98%, increased the abundance of Olsenella, Alistipes and Alloprevotella, and decreased the abundance of Helicobacter and Mucispirillum in mice with diabetic cardiovascular disease[57].

Another study assessed the effect of canagliflozin on the gut microbiota and the serum concentrations of gut-derived uremic toxins in 5/6th nephrectomized (Nx) rats[58]. Canagliflozin improved the concentration of Lactobacillus bacteria, a bacterium which is known to have the ability to maintain the

expression of tight junction proteins and thereby prevent the accumulation of uremic toxins in the serum of chronic kidney disease patients. Indeed, this study showed that canagliflozin increased the expression of the tight junctions' proteins in the ascending colon which were low in the Nx rats. Consequently, the serum concentration of gut-derived uremic toxins which were significantly elevated in the Nx rats were lowered significantly by Canagliflozin[58].

Based on the literature evidence summarized above, SGLT-2 inhibitors have a positive impact on the gut microbiota. It is well known that SGLT-2 inhibitors are effective in treating DM and in providing CV protection. Future studies are awaited to understand whether these beneficial effects are in part due to their action on the gut microbiota.

PPAR AGONISTS

PPAR gamma, a nuclear receptor is vastly present in the colon[59] where it is involved in the intestinal cell metabolism, differentiation and inflammation[60]. It is closely linked to various pathological conditions including diabetes which is linked to the gut microbiota. Evidence shows the PPAR gamma agonists can help reduce gut inflammation, colon cancer and diabetes[61,62]. PPAR-gamma activity has been shown to be induced by gut microbiota. A study in humans assessed the involvement of various gut bacterial strains belonging to the major phyla such as Firmicutes, Bacteroides, Actinobacteria and Fusobacteria on PPAR gamma activity located within the intestinal epithelial cells[63]. These bacteria were anaerobically cultured and a specific reported cell line called HT-29-PPAR gamma was used to identify the bacteria with PPAR gamma activity regulation. At the level of phyla, Firmicutes and Fusobacteria showed the strongest effect while Actinobacter showed mild to no effect. Roseburia hominis and Roseburia intestinalis within the Firmicutes phyla and Fusobacterium naviforme within the Fusobacteria phyla exhibited the strongest capacity to stimulate PPAR gamma activity.

As shown above, an agonistic effect on PPAR gamma receptors that are widely present throughout the colon, can have a positive impact on gut health. However, the current evidence is limited, and it is compounded by the infrequent use of medications belonging to this class. Hence, it will be interesting to see if future studies look more closely into the relationship between PPAR gamma receptor agonism and gut microbiota.

ALPHA GLUCOSIDASE INHIBITORS

SCFA's, including butyrate play an important role in pathophysiology of diabetes. Patients with T2DM have a decline in the abundance of butyrate-producing bacteria[64]. Acarbose has shown to increase the serum butyrate levels in patients with impaired glucose tolerance. Oral supplementation of butyrate in mice, has shown to improve insulin sensitivity and increase energy expenditure *via* mitochondrial action[65]. Zhang *et al*[66] performed a study in 52 Chinese patients with prediabetes, who were assigned randomly to receive either acarbose or placebo, to characterize the gut microbiota. The baseline gut microbiota composition in the fecal samples of these prediabetic patients showed an abundance in the genera Bacteroides (19.4%) and Faecalibacterium (8.97%), and an abundance in Firmicutes (68.53%), Bacteroidetes (27.85%), Protobacteria (1.98%) and Actinobacteria (0.98%) at the level of phyla. Acarbose treatment led to an enrichment in five genera, including Lactobacillus and Dialister and there was a corresponding decline in six genera, including Butyricicoccus, Phascolarctobacterium, and Ruminococcus[66]. The same study also showed that some species of Megasphaera thrived following acarbose treatment. This species has shown to have many beneficial effects such as conversion of carbohydrates to SCFA's, including butyrate, acetate, valerate and formate. It also utilizes lactate, a harmful end product of carbohydrate metabolism and converts it into SCFA's, including propionate, acetate and butyrate[67].

SULFONYLUREAS

The data so far, suggest a lack of positive effect on the gut microbiota by the use of sulfonylurea. In one study, type 2 diabetic patients treated with metformin were randomized to receive either gliclazide or dapagliflozin to analyze their effect on gut microbiome. At the end of 12 wk, neither treatment significantly changed the gut microbiome alpha diversity or composition[68].

Bile acid metabolism and signaling is important for maintaining metabolic health. Changes in the composition and content of plasma bile acids are seen in patients with diabetes and/or obesity[69]. Gu Y *et al*[70] assigned treatment-naïve type 2 diabetes patients to receive either acarbose or glipizide to analyze the plasma bile acids and choose the appropriate anti-diabetic medication for treatment. Acarbose, but not glipizide, led to an increase in the ratio between primary bile acids and secondary bile acids. In the same study, acarbose caused an increase in the abundance of Lactobacillus and Bifidobac-

terium in the gut microbiota[70].

The lack of an alteration in the gut microbiota by sulfonylureas may be partly due to the limited studies that have investigated its role in gut health. However, current literature has shown no organ protection action including cardiovascular protection from the use of a sulfonylurea. This poses a question about its role in gut health and future studies are needed for a better clarification.

CONCLUSION

Recent studies have remarkably improved understanding of the role of the gut microbiota in the pathophysiology of T2DM and metabolic diseases. The role of dysbiosis in the various pathophysiological mechanisms related to altered metabolism of SCFAs, interaction with gut hormones, increased gut microbial metabolite TMAO and endotoxemia in the pathogenesis of T2DM and cardio-metabolic diseases have been demonstrated in numerous studies. The impact of gut microbiota on the therapeutic effects of anti-diabetic medications is becoming increasingly recognized. Altering the gut microbiota is proposed as an attractive method to decrease inflammation and weight gain, improve glucose homeostasis, and prevent cardio-metabolic diseases. The current review has outlined the role of the microbiota in the pathophysiology of T2DM and highlighted the interplay between anti-diabetic medications, the microbiota and some of the known pathophysiological mechanisms. In future, the gut microbiota may be a novel target for new drug development to prevent and treat T2DM and metabolic diseases. However, further studies are needed prior to successful clinical application of gut microbiota modulation.

FOOTNOTES

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MINIREVIEWS

Reinfection, recontamination and revaccination for SARS-CoV-2

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Abstract

The reports on coronavirus disease 2019 (COVID-19) describe the pandemic in waves. Similar to the ocean's waves, the frequency and amplitude of the number of new cases and the number of deaths were globally quite regular; nevertheless, they showed important regional irregularities and the direction of spread has been generally rather unpredictable for COVID-19. One of the major reasons for the repeated outbreaks is the mutating capacity of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that allows the virus to infect persons who have natural immunity or have been vaccinated. Vaccination began in vast campaigns from the second year of the pandemic that was supposed to decrease the magnitude of the waves. Although it reduced the complications, the expected attenuation of the disease expansion has not yet been met. This paper provides a short overview of the most recent data on the rate of reinfection in vaccinated and non-vaccinated individuals. It points out that testing positive for a second time for SARS-CoV-2 does not necessarily mean a reinfection; it can also be interpreted as recontamination. The symptom free outcome as well as the rapid reconversion of the polymerase chain reaction test may help to determine the difference between reinfection and recontamination. Awareness of this phenomenon may be valuable in times of human resource difficulties. The available evidence may suggest that the protective value of a prior infection could be better considered for vaccine distribution in the future.

Key Words: SARS-CoV-2; COVID-19; Polymerase Chain Reaction; Immunisation; Contamination; Vaccination

Core Tip: Reinfection: There is not enough evidence of the protective efficacy of the natural immunity induced by a primary infection with severe acute coronavirus 2 (SARS-CoV-2). Recontamination: Testing positive for a second time for SARS-CoV-2 does not necessarily mean a reinfection; it can also be interpreted as recontamination. Revaccination: The available evidence may suggest that the protective value of a prior infection could be better considered for vaccine distribution in the future.

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INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infected more than 400 million people worldwide and caused the death of over 6 million[1]. In the last two years SARS-CoV-2 has become the most common cause of death from a single infectious pathogen, preceding *Mycobacterium tuberculosis*, responsible for an estimated 1.4 million victims in 2019[2] and human immunodeficiency virus and malaria, the mortality of which was below 1 million in the last years[3].

The majority of deceased people were retired Caucasians[1]. The geography of the disease expansion may explain why coronavirus, which was most devastating in North America and Europe, received outstanding media and political attention in comparison to other infections with high mortality even if these infections affect young people as much as the elderly. Reports directly showing patients with respiratory assistance in hospital intensive care units were seen by many people for the first time. Beyond the statistical data these widely diffused images contributed to the shocking experience of the pandemic. Coronavirus disease 2019 (COVID-19) is the first pandemic in history to be broadcast live from the beginning on.

There is no efficacious treatment for COVID-19. Hospitalisation may help in those who require oxygen supplementation and in the care of some complications of the disease. Vaccines of different types have been developed to provide protection against infection. This occasion was a world first for the mRNA vaccines[4,5] and the first adenovirus-based vaccine authorized by the US Food and Drug Administration[6]. To date their efficacy in the prevention of severe complications of COVID-19 is evident but their power to reduce disease spread has not met expectations[1].

REINFECTION

The first reinfection by a different strain of SARS-CoV-2 was identified in the summer of 2020 with whole genome sequencing and comparative genome analysis in an immunocompetent person with an interval of 142 d between the two episodes[7]. In this case, the primary infection was symptomatic and the reinfection was asymptomatic. A larger analysis of several cases found that the reinfection may be either less severe, or may also have a more severe outcome as compared to the primary infection[8].

When the vaccinations started in spring 2021, follow-up of the protective effect of recovering from a primary infection became problematic, as the promotion of vaccination was so strong in most affected countries, that the majority of the people were vaccinated. Nevertheless, there are some publications available that may help elucidate this issue.

No symptomatic reinfection was detected in 1265 British health care workers who had been followed with positive anti-spike-IgG for 31 wk[9]. In the national, federated database of Qatar there were 350.000 polymerase chain reaction (PCR)-confirmed infections registered between 28 February 2020 and 28 April 2021. Among these cases 1300 reinfections were identified and these cases were matched with primary infections in a 1:5 ratio. The numbers of severe, critical and fatal cases were 158, 28 and 7 for primary infections and 4, 0 and 0 for reinfections, respectively. Vaccinated persons were excluded from the analysis. Severe outcome meant hospitalisation and critical outcome meant hospitalisation in the intensive care unit[10].

These data support the hypothesis that recovering from a primary SARS-CoV-2 infection yields natural immunity that protects from both, potential reinfection and the severe complications of a reinfection. However, vaccinations were declared to provide additional protection.

Breakthrough infections in vaccinated individuals and in those who had a prior infection were compared in the same Qatar database. The PCR cycle threshold is known to inversely correlate with viral load. Or, the cycle threshold value is 1.3 cycles higher for breakthrough infections following the BNT162b2 vaccine, 3.2 cycles higher for breakthrough infections following the mRNA-1273 vaccine, and 4.0 cycles higher for reinfections in unvaccinated individuals than at primary infection. Thus,

unvaccinated persons who recovered from a prior SARS-CoV-2 infection had the lowest viral load during a breakthrough infection as compared to their mRNA vaccinated counterparts[11]. In a Bangladesh cohort including 1644 participants, the naturally infected population was less likely to be reinfected by SARS-CoV-2 than the infection-naïve and vaccinated participants with one of the seven different vaccines authorised in this country[12]. A Danish study of 3.800 blood donors who had SARS-CoV-2 PCR positivity found no evidence of a decline in the proportion of detectable anti-SARS-CoV-2 antibodies over time up to 15 mo[13].

In contrast, in a study of 150.000 patients who had recovered from COVID-19 in Israel, those who were vaccinated had a lower risk of reinfection than those who were not vaccinated. The difference was smaller in the elderly population. The study did not report on the severity of the reinfections. The authors recognise that the lack of assessment of disease severity and hospitalisation is an important limitation of their work[14].

RECONTAMINATION

The second contact with SARS-CoV-2 is not necessarily a second infection and may only be a contamination, which means that some of the pathogen may be present on the body surface or mucus membrane. However, the invasion of adjacent tissues does not follow, as the person's defence system prevents it.

Someone contaminated with SARS-CoV-2 will have a positive test, and may possibly and transitionally transmit the virus but will remain asymptomatic. However, the duration of the positivity of a contaminated individual following primary infection or vaccination will be presumably short. In our experience, the duration of their positivity is around 5 d (unpublished data) as compared to the positivity of healthy individuals who undergo a first infection which is at least 8-20 d.

This is in reality what we may expect from the protective efficacy of vaccinations and natural immunity. They do not inhibit the virus reaching the nasal mucosa when in contact with an infected patient. Nevertheless, they provide a more reactive immunity that helps in preventing the development of the disease within the body.

The possible interpretations of a positive SARS-CoV-2 PCR test are summarised in Table 1. Under the pressure of the pandemic it may be difficult to accept that interpretation of the tests depend on the clinical situation; moreover, if the clinical context is omitted, decisions based exclusively on test results may be harmful. The importance of the correct interpretation of sustained PCR positivity at primary infection has been stressed, particularly in the case of comorbidities needing rapid treatment such as certain malignancies[15]. The authorisation of asymptomatic health care workers to return to work has become routine in many hospitals facing problems of human resources. Some other situations when a positive PCR test may be disturbing are listed in Table 2.

REVACCINATION

Initially, producers affirmed that two doses one month apart provide immunity for SARS-CoV-2, with the exception of Ad26.COV2-S with which one dose is equivalent to two doses of the other products. However, the level of protective antibodies was found to decrease with time; therefore, the potential necessity for a booster dose was discussed. It is important to note, that the waning of immunity was studied in vaccinated populations whereas for naturally immunised populations there are only observations from case series[16].

Currently, in most Western countries a booster is required 6 mo after the first vaccination for official recognition of protection. The suggestion that the booster may or should be different from the primary vaccine adds to the confusion related to the efficacy of each single vaccine. We agree with the WHO's consideration that in view of the shortage of vaccines, assuring booster doses for some populations may increase the possibility that other populations will miss even the primary vaccination[16].

In addition, the above-mentioned results[11,12,13] show that natural immunity may even be stronger and last longer than the effect of vaccination depending on both the severity of the infection and the type of vaccination. The distribution of vaccines to non-infected individuals rather than to naturally immunised individuals would probably have saved more lives and would certainly have been more equitable. This hypothetical redistribution would have concerned hundreds of millions of people.

DISCUSSION

One of the destabilising lessons of the pandemic is that scientific predictions concerning COVID-19's clinical presentation and geographical expansion were rarely correct.

Table 1 Possible meaning of a positive polymerase chain reaction test for severe acute respiratory syndrome coronavirus 2

Test result	Meaning
True positive result	Asymptomatic infection with SARS-CoV-2
True positive result	Symptomatic infection with SARS-CoV-2 (COVID-19)
Sustained positive result	Carriage of virus particles after recovering from COVID-19
False positive result	No infection with SARS-CoV-2
Repeatedly positive result	Reinfection with SARS-CoV-2
Repeatedly positive result	Recontamination with SARS-CoV-2

COVID-19: Coronavirus disease 2019; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2.

Table 2 Possible situations, when the misinterpretation of contamination with severe acute respiratory syndrome coronavirus 2 may cause unfair disadvantage for the tested individual

Situations where symptom-free persons can be tested
Being a contact of an infected person
Infection control in a health care or social institution
Starting a new job
Travelling abroad
Participating at a controlled event

Measures seeming reasonable at one point may be completely useless a couple of weeks later and vice versa. For instance, the nationwide testing in Slovakia in the winter of 2020 drew international attention and the identification of a high number of asymptomatic infections gained recognition. It was assumed that containment of the detected individuals would prevent disease spread. Nevertheless, the country could not avoid the explosion of the disease and the burden on its healthcare system. In contrast, Sweden was much criticised for its liberal management of the pandemic and had a relatively high mortality rate in the first months; however, many more restrictive countries had worse outcomes one year later[1].

Decision making and observance of the prevalence are even more unpredictable than the behaviour of the virus. Decision makers are challenged with opposing expectations but miss essential references. They have to solve dilemmas such as protecting the lives of the elderly *vs* the jobs of the young or the equitable distribution of the vaccines *vs* the most rapid care of their own population. On the other hand observance supposes explanations and never meant obedience.

With the arrival of the Omicron strain there is some hope that after more than two years the disease will pass in a more controllable phase.

CONCLUSION

(1) Differentiation between recontamination and reinfection may be useful for persons testing positive for SARS-COV-2 by PCR; (2) The protective effect of prior infection should be considered before vaccination against COVID-19; and (3) Fairness in vaccine distribution should be respected at the global scale.

FOOTNOTES

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ORIGINAL ARTICLE

Prospective Study

Are we aware of radiation: A study about necessity of diagnostic X-ray exposure

Erdal Karavas, Bunyamin Ece, Sonay Aydın, Mehmet Kocak, Zeliha Cosgun, Isil Esen Bostanci, Mecit Kantarci

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Abstract

BACKGROUND

Total exposure to ionizing radiation has nearly doubled in the last two decades. This increase is primarily due to increased computed tomography (CT) exposure. Concerns have been raised about the risks associated with patients' exposure to medical imaging radiation, which can increase a person's lifetime risk of developing cancer. Preventing unnecessary examinations becomes critical at this point. To avoid unnecessary examinations, it is necessary to understand the demanding process.

AIM

To ascertain clinicians' awareness of and reasons for requesting a CT examination.

METHODS

We developed an online questionnaire that included 20 questions about clinicians' awareness of radiation safety and their reasons for requesting a CT examination, as well as demographic information such as age, gender, and year of medical practice experience. Additionally, we asked participants the number of CT scans requested in a month, the patients' questions and approaches about the imaging

method, the effect of the patient's previous imaging history on the current imaging request, whether they believed that they had sufficient information about radiation doses, and whether they requested CT without an indication. We administered the questionnaire to clinicians from a variety of different professions in four different cities.

RESULTS

A total of 195 clinicians participated. Internal medicine specialists were the most crowded group (38/195, 19.5%). Mean age of the population was 33.66 ± 5.92 years. Mean year of experience was 9.01 ± 5.96. Mean number of requested CT scans in a month was 36.88 ± 5.86. Forty-five (23.1%) participants stated that they requested CT scans without clinical indication. The most common reasons for CT scan requests were work load, fear of malpractice, and patient demand/insistence.

CONCLUSION

CT scan requests are influenced by a variety of factors, both internal and external to the doctors and patients. Raising awareness of radiation safety and reducing fear of malpractice by limiting the number of patients per physician may result in a reduction in unnecessary CT examinations and ionizing radiation exposure.

Key Words: Ionizing radiation; Exposure; Tomography; Physicians; Knowledge; Awareness

Core Tip: Total exposure to ionizing radiation has nearly doubled in the last two decades. This increase is primarily due to increased computed tomography (CT) exposure. Preventing unnecessary examinations becomes critical. We developed an online questionnaire about clinicians' awareness of radiation and their reasons for requesting a CT scan. The most common reasons for CT scan requests were work load, fear of malpractice, and patient demand/insistence. CT scan requests are influenced by a variety of factors. Raising awareness of radiation and reducing fear of malpractice by limiting number of patients per physician may result in a reduction in unnecessary CT examinations and radiation exposure.

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INTRODUCTION

Normally, natural exposure to small doses of radiation is inherent in life. The average exposure is approximately 3 mSv/year. On average 2.4 mSv of the annual dose is due to radon and naturally-occurring radiation sources (natural background radiation) and 0.6 mSv is due to the man-made medical imaging and treatment methods[1].

Today, due to the development of technology and clinicians' easy access to medical imaging, ionizing radiation is one of the most used methods in diagnosis and treatment of diseases in daily practice[2-4].

Radiation is a potential carcinogen affecting many patients undergoing medical imaging worldwide. Total exposure to ionizing radiation has nearly doubled in the last decades. This increase is primarily the result of increased exposure from computed tomography (CT), nuclear medicine, and interventional fluoroscopy[5,6]. Concerns have been expressed about the risks associated with patients' exposure to medical imaging radiation[7,8]. Ionizing radiation exposure can damage DNA, increasing an individual's lifetime risk of developing cancer. The radiation doses associated with routine CT examinations are comparable to those received by individuals with a documented increased risk of cancer. For example, an increased risk of cancer has been identified in long-term survivors of the Hiroshima and Nagasaki atomic bombings who were exposed to 10 to 100 millisieverts of radiation[9,10]. A single CT scan can expose patients to an equivalent amount of radiation, and patients may undergo multiple CT scans over time[11,12]. While a single medical imaging exam with radiation does not pose a significant risk to an individual, the annual exposure to radiation from millions of imaging examinations with radiation is a significant public health problem. Additionally, accidental exposure to high doses of ionizing radiation can also result in short-term injuries, including burns and hair loss. Exposure to such doses directly in the eyes can increase the risk of developing cataracts[13,14].

In these days, the incidence of radiation exposure from medical imaging will continue to rise exponentially for several reasons. First, medical imaging technology has allowed physicians to evaluate easily and quickly both anatomy and function. Thereby, medical imaging provides benefits such as increased confidence of clinicians' decision, patient management, and protection from malpractice. In addition, patients are demanding more tests to ensure correct diagnosis and treatment[5].

Preventing unnecessary medical imaging examinations is an option to reduce total exposure to radiation. To avoid unnecessary examinations, it is necessary to understand the demanding process. At this point, concerns have also been raised that clinicians may lack important information in ordering medical imaging exams that use radiation. Clinicians may not have access to patients' medical imaging history or radiation dose history. Due to insufficient information, clinicians may unnecessarily order imaging procedures that have already been conducted. Additionally, if clinicians see a record of the total radiation dose to patients' previous medical history, such information might influence clinicians' decision to order a medical imaging test with radiation. Sometimes clinicians may be unaware or have insufficient knowledge of recommended criteria about whether medical imaging testing will be effective in their medical decision. As a result, clinicians may request unindicated medical imaging tests and unnecessarily expose patients to radiation[14,15].

In this study, we aimed to learn about the radiation awareness of clinicians and their reasons for requesting medical imaging tests with radiation through a questionnaire.

MATERIALS AND METHODS

We developed a 20-question questionnaire for clinicians to evaluate radiation awareness and the reasons for requesting radiation-containing tests. The content of the questionnaire is shown in Supplementary material.

We sent the online invitation to participate in the questionnaire to 500 clinicians from various specialties in four different cities. Of those who were invited, 195 participated in the questionnaire.

The study was designed as a descriptive cross-sectional study and local ethics committee approval was obtained for this study.

Questionnaire content: The first four questions of the 20-question survey inquired about the clinician's specializations, age, experience in medical practice, and professional title. In question 5, we inquired as to whether participants believed they had sufficient information about radiation doses. Questions 6-8 were designed to ascertain participants' level of knowledge about radiation dose. In question 9, the number of CT scans requested by clinicians in a month was asked. Questions 10-12 were designed to evaluate the patient's questions and approaches about the imaging method. Questions 13-16 were designed to investigate the effect of the patient's previous imaging history on the current imaging request. The 17th question inquired about the factors that can affect clinicians' CT request. The 18-20th questions were prepared for the purpose of analysis regarding the CT request that was made without indication Supplementary material.

Statistical analysis: Data were analyzed using the Statistical Package for Social Sciences (SPSS) for Windows 20 software (IBM SPSS Inc., Chicago, IL, USA). Conformity of the data to normal distribution was assessed by the Kolmogorov-Smirnov test. Numerical variables with a normal distribution are shown as the mean ± standard deviation (SD) values, variables without a normal distribution as median (minimum-maximum) values, and categorical variables as number (*n*) and percentage (%). Chi-square test was used to analyze the difference of the answers according to gender, title, profession, and year of experience of the participants. A value of $P < 0.05$ was regarded as statistically significant.

RESULTS

A total of 195 clinicians from four different cities participated in the questionnaire. The participants' mean age was 33.6 ± 5.9 (24-56) years. Their mean years of medical practice was 9.0 ± 6.0 (1-28) years. Approximately 64.1% of the participants were specialists, 26.2% were research assistants, and 9.7% were general practitioners. The participants were from various specialties, with internal medicine doctors accounting for the highest percentage at 19.5%. Descriptive data is shown in Table 1.

One hundred and fifty-nine (81.5%) of the participants stated that they did not feel sufficient about radiation knowledge.

The answers to the questions asked to ascertain participants' level of knowledge about radiation dose are given in Table 2. According to these results, in the 6th-7th-8th questions, respectively 60.2%, 60%, and 79.5% of participants underestimated and respectively 12.8%, 22.6%, and 0% of participants overestimated the radiation dose rates of the examinations.

Mean number of requested CT scans in a month was 36.88 ± 5.86 (1-300). Among the participants, the specialties with the most CT requests per month were emergency medicine (mean, 82), general surgery (mean, 76), and neurosurgery (mean, 57).

Table 1 Some characteristics of the physicians participating in the study

Characteristic of physicians		*n* (%)
Medical department of physicians	Internal Medicine	38 (19.5)
	Emergency Medicine	35 (17.9)
	General Surgery	25 (12.8)
	Cardiology	14 (7.2)
	Anesthesiology	12 (6.2)
	Urology	11 (5.6)
	Pulmonology	10 (5.1)
	Orthopedic Surgery	10 (5.1)
	Child and adolescent psychiatry	7 (3.6)
	Neurosurgery	6 (3.1)
	Neurology	6 (3.1)
	Others	18 (9.2)
Age group, yr	24-30	68 (34.9)
	31-40	99 (50.8)
	> 40	28 (14.3)
Medical practice duration, yr	≤ 5	62 (31.8)
	6-10	69 (35.3)
	11-15	28 (14.4)
	>15	36 (18.5)
Degree of physician	Specialist doctor	125 (64.1)
	Research assistant	51 (26.2)
	General practitioner	19 (9.7)
Total		195 (100)

Others: Pediatrics, medical oncology, forensic medical specialist, otolaryngologist, family physician, gynecology and obstetrics, ophthalmology, dermatology, physical therapy, and rehabilitation.

There was no statistically significant difference between duration of medical practice experience and monthly CT requests (P = 0.385).

The proportions of the answers given to the 10-12th questions evaluating the patient's questions and approaches about the imaging method, as well as to the 13-16th questions investigating the effect of the patient's previous imaging history on the current imaging request are shown in Table 3. The most commonly mentioned causes were found to be indication, concern about failure to diagnose, and fear of malpractice (Table 4).

About 24.6% of the participants stated that they requested CT even though there was no clinical indication. The reasons for requesting CT even though there is no clinical indication are shown in Table 5. The most common reasons were the desire to complete the diagnosis quickly, the patient's demand, and fear of malpractice.

The answers given to the question of what should be done to prevent CT examinations without indication are shown in Table 6. The most frequently stated response of the participants (67.2%) was "reducing the patient density and allocating sufficient time for doctors to examine patients".

DISCUSSION

Estimating the dose rates of examinations is a frequently used technique in questionnaire studies to assess participants' knowledge and awareness of ionizing radiation. For this purpose, posteroanterior chest radiography which is frequently used in clinical practice and a daily radiation dose encountered in nature can be taken as a basis[16]. In this way, the opinions of the participants about the radiation doses

Table 2 Participants' estimates of radiation dose

Radiation dose estimation		*n* (%)
Standard CT equivalent chest X-ray	10 ×	12 (6.2)
	50 ×	30 (15.5)
	100 ×	75 (38.5)
	500 ×[a]	53 (27.2)
	1000 ×	25 (12.8)
Comparison of chest X-ray with the daily average amount of radiation in nature (cosmic rays, earth and underground sources, *etc.*)	1 d	71 (36.4)
	3 d	46 (23.6)
	7 d[a]	34 (17.4)
	15 d	44 (22.6)
Comparison of abdominal and pelvic CT with the daily average amount of radiation in nature (cosmic rays, earth and underground sources, *etc.*)	6 mo	30 (15.4)
	1 yr	60 (30.8)
	2 yr	65 (33.3)
	4 yr[a]	40 (20.5)
Total		195 (100)

[a]Correct answer. CT: Computed tomography.

Table 3 Patient questions and approach to imaging and consideration of previous computed tomography scans and radiation dose among physicians

Patient questions about radiation and physicians' consideration of previous radiation dose		*n* (%)
Informing the patient about radiation		94 (48.2)
Patients questioning radiation dose and harm		78 (40.0)
Frequency of patients asking questions about radiation dose and harm	Rarely	26 (13.3)
	Sometimes	44 (22.6)
	Mostly	8 (4.1)
Physicians checking old imaging		180 (91.8)
CT request affected if more than 10 CT scans were performed in the last 2 years		65 (33.3)
Easier CT request if less than 10 CT scans were performed in the last 2 years		64 (32.8)
Physicians affected by the last 2 yr of CT dose seen over the hospital system		130 (66.7)

CT: Computed tomography.

of the examinations used in clinical practice can be reached. The majority of participants in our study underestimated the dose rates of examinations. In the literature, in a survey study conducted with research assistants, Koçyiğit *et al*[17] found that 64.9% of participants underestimated the radiation dose associated with abdominal CT examinations and 58.8% underestimated the radiation dose associated with abdominal radiography. Ataç *et al*[18] in their questionnaire study with radiology workers, found that the majority of participants underestimated the dose value and dose rate questions. Lee *et al* in their questionnaire study among non-radiologists, found that 77% of participants underestimated the radiation dose for a chest X-ray[19]. The findings of our study and similar findings in the literature lead us to believe that participants' underestimation of the dose contents may be a factor in facilitating the request for medical imaging examinations with ionizing radiation.

In our study, we found that 48.2% of patients were informed about radiation prior to requesting an examination containing ionizing radiation. There are also studies in the literature demonstrating that the sharing of radiation risk information between clinicians and patients is rare[20-22]. One possible

Table 4 Factors affecting computed tomography request

Factors affecting CT request[a]	*n* (%)
Indication (Mandatory requirement)	192 (98.5)
Patient's age	68 (34.9)
Patient's insistence or request	22 (11.3)
Having a large number of patients	13 (6.7)
Concern about doing malpractice	70 (35.9)
Concern about not being able to diagnose	82 (42.1)

[a]A physician was able to give more than one answer. CT: Computed tomography.

Table 5 Requesting computed tomography without clinical indication

Requesting CT without clinical indication		*n* (%)
CT request without clinical indication		48 (24.6)
Causes of CT request without clinical indication (n = 48)	Patient's insist or request	21 (10.8)
	Having a large number of patients	8 (4.1)
	Worry about doing malpractice	20 (10.3)
	Concern about not being able to diagnose	16 (8.2)
	Desire to complete diagnosis quickly	23 (11.8)
	Length of US and MRI appointment times	14 (7.2)

CT: Computed tomography; US: Ultrasound; MRI: Magnetic resonance imaging.

Table 6 Measures to be taken to prevent computed tomography request without indication

Measures to be taken to prevent CT request without indication	*n* (%)
Reducing patient demand	85 (43.6)
Educating physicians about CT radiation dose	61 (31.3)
Extending the patient examination time	131 (67.2)
Shortening US and MRI appointment times	23 (11.8)

CT: Computed tomography; US: Ultrasound; MRI: Magnetic resonance imaging.

explanation for this low rate may be the high patient density which results in insufficient time to give detailed information to the patient. Additionally, there are studies in the literature showing that clinicians are uncomfortable sharing radiation risk information with patients[23]. In our study, the rate of asking questions by patients about radiation dose or potential harm in examination containing ionizing radiation was found to be as low as 40%. This result could be interpreted as the patient's low awareness of radiation exposure. Informing patients about the potential risks of radiation is left to the radiology units in many hospitals. However, after the imaging examination is requested by the clinician, the patient comes to the radiology unit to perform the desired examination, so it is not possible for the patient to think about the subject again. It is also emphasized in the FDA White Paper that informed clinical decision making together with the clinician doctor during the clinical examination will be more effective[14]. By informing patients about radiation exposure associated with imaging methods and increasing their awareness, it may be possible to reduce unindicated and unnecessary CT scans[24,25]. In the literature, it has been stated that awareness of radiation exposure has increased with the participation of patients and doctors in courses on radiation[26-28]. In addition, Sullivan *et al*[29] demonstrated that short-term and repetitive refresher training had a positive effect on raising awareness of radiation.

In our study, while the mean number of requested CT scans in a month was 36.9 ± 5.86, 81.5% of the participants stated that they did not feel sufficient about radiation knowledge. These findings are significant because they demonstrate a lack of competence about radiation information despite the frequency of CT demand as an imaging method in daily practice. In the literature, it is seen that while participants express growing concern about the risk of cancer caused by ionizing radiation, they have insufficient information about how much radiation the patient is exposed to[30,31].

In our study, it is important that a very large part of the participants (91.8%) reviewed the previous examinations before requesting a radiation-containing examination and that a significant portion (66.7%) would be affected by the high dose warning in the hospital system record. These results can be accepted as an indicator that physicians' attention can be increased with the help of assistive methods integrated into the hospital system, regarding the request for examinations containing radiation. Again, based on these results, doctors' inability to access medical imaging containing radiation performed in different health centers may be a factor in the procedure's unnecessary repetition.

The factors affecting participants' decisions to request a CT scan were examined in our study. The great majority of the participants stated the option of indication as the main factor and primary reason for requesting CT. It has been understood that options such as the concern about not being able to diagnose, the worry about doing malpractice, the high patient density and patient's insistence or request are significantly effective in requesting CT. Due to these various factors, it is inevitable that there will be an increase in CT requests, unnecessary/unindicated CT scans, and ionizing radiation exposure. It is important that the desire to make a diagnosis quickly and the concern for malpractice are frequently seen among the reasons for requesting CT even though there is no clinical indication. Additionally, it is important that the majority of the participants believe that patient density should be reduced and examination times should be extended in order to prevent non-indication CT scans. Yıldız *et al*[32] reported in their study in the emergency department that CT was frequently used in childhood head traumas, but normal imaging results were obtained in 98.5%. Additionally, they emphasized the need to prioritize clinical decision-making rules and patient follow-up for CT request. Dağlar *et al*[33] evaluated 51.2% of CT examinations performed for spine and pelvis evaluation as normal CT in their study. They emphasized that due to this high rate, precautions should be taken for unnecessary CT use. Karavas *et al*[34] stated that unnecessary CT requests may result in an increase in workload and patient density in radiology units, and related problems in reporting and an increase in diagnostic errors. We think that providing the opportunity to spend more time on clinical examination by limiting the number of patients per physician will help reduce fear of malpractice, avoid unnecessary CT examinations, and reduce ionizing radiation exposure.

According to the findings of our study, some solutions can be offered to prevent unnecessary radiation exposure. The first and most critical of these is to raise patients' and clinicians' radiation awareness and consciousness, and to schedule regular radiation training sessions. If the patient's previous radiation exposure and total dose of exposure are displayed as warnings in the patient information system in the hospital before clinicians make a request for a medical exam that includes radiation, this can help reduce unnecessary request and exam repetition. By reducing patient density, doctors can spend more time with the patient rather than rushing to a CT diagnosis, and radiation exposure can be reduced. Additionally, with detailed informed consent to the patient about the potential risks of radiation, the patient's insistence on examination with radiation is reduced, and unnecessary radiation exposure can be prevented.

Our study has some limitations, such as the low number of participants and the fact that the participating clinicians are from different specialties. However, a heterogeneous sample with diversity was created by providing participants from various cities and hospitals. There may be variations in practice based on the participants' specializations and whether they provide emergency or outpatient care. However, the study's primary objective was not to analyze these differences, but to provide an overview of ionizing radiation awareness. Additionally, the questionnaire is a test method and contains closed-ended questions, which is also a limitation of the study.

CONCLUSION

As a result of our study's findings, both patients and physicians have a low level of knowledge and awareness about ionizing radiation. While the primary consideration when requesting a radiation-containing imaging method is the indication, other considerations such as concern about not being able to diagnose, worry about doing malpractice, high patient density, and the patient's insistence also factor in. Desire to complete diagnosis quickly and fear of malpractice may be the reasons for unindicated CT demand and increase exposure to ionizing radiation. Unnecessary and unindicated ionizing radiation exposure can be reduced by reducing patient density in daily practice, extending examination times, and improving hospital systems in a way that allows for detailed documentation of the patient's previous radiation doses. Thus, potential risks to the patient associated with radiological imaging and ionizing radiation exposure can be minimized.

ARTICLE HIGHLIGHTS

Research background

Radiation-containing imaging and treatment techniques are frequently used in daily clinical practice. The advancement of technology and clinicians' increased access to radiation-containing examinations also expand the applications of radiation-containing examinations. Recently, the use of radiation-based medical exams has increased exponentially. The dangers of radiation should be highlighted, and awareness of radiation should be increased.

Research motivation

Radiation is a potential carcinogen. Ionizing radiation exposure can damage DNA, increasing an individual's lifetime risk of developing cancer. Medical exams containing radiation are sometimes unnecessary and overused. Preventing unnecessary medical imaging examinations is an option to reduce total exposure to radiation. To avoid unnecessary examinations, it is necessary to understand the demanding process.

Research objectives

To increase radiation awareness and thus reduce unnecessary radiation exposure.

Research methods

We developed a 20-question questionnaire for clinicians to evaluate radiation awareness and the reasons for requesting radiation-containing tests.

Research results

Most of the participants stated that they did not feel sufficient about radiation knowledge and the majority of participants underestimated examination dose rates. Both patients and physicians had a low level of knowledge and awareness about ionizing radiation. In our study, we found that 48.2% of patients were informed about radiation prior to requesting an examination containing ionizing radiation. A large part of the participants (91.8%) reviewed the previous examinations before requesting a radiation-containing examination and that a significant portion (66.7%) would be affected by the high dose warning in the hospital system record. Indication, concern about not being able to diagnose, worry about doing malpractice, high patient density, and the patient's insistence are various factors in requesting a radiation-containing imaging method. Desire to complete diagnosis quickly and fear of malpractice may be the reasons for unindicated computed tomography (CT) demand.

Research conclusions

According to the findings of our study, some solutions can be offered to prevent unnecessary radiation exposure. The first and most critical of these is to raise patients' and clinicians' radiation awareness and consciousness, and to schedule regular radiation training sessions. If the patient's previous radiation exposure and total dose of exposure are displayed as warnings in the patient information system in the hospital before clinicians make a request for a medical exam that includes radiation, this can help reduce unnecessary request and exam repetition. By reducing patient density, doctors can spend more time with the patient rather than rushing to a CT diagnosis, and radiation exposure can be reduced. Additionally, with detailed informed consent to the patient about the potential risks of radiation, the patient's insistence on examination with radiation is reduced, and unnecessary radiation exposure can be prevented.

Research perspectives

Following radiation awareness training for patients and clinicians and the addition of a total radiation dose warning to the hospital's patient information system, prospective studies can be conducted to determine whether the number of requests for radiation-containing examinations has decreased in certain centers.

FOOTNOTES

Author contributions: Karavas E, Ece B, and Aydin S participated in design and oversight of the study, and drafted the manuscript; Ece B and Aydin S assisted with data analysis; Kocak M, Cosgun Z, Bostanci I, and Kantarci M participated in design of the study, and was involved in data collection; all authors wrote, read, and approved the final manuscript.

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ORIGINAL ARTICLE

Prospective Study

Robotic ultrasound: An initial feasibility study

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Abstract

BACKGROUND

Performing ultrasound during the current pandemic time is quite challenging. To reduce the chances of cross-infection and keep healthcare workers safe, a robotic ultrasound system was developed, which can be controlled remotely. It will also pave way for broadening the reach of ultrasound in remote distant rural areas as well.

AIM

To assess the feasibility of a robotic system in performing abdominal ultrasound and compare it with the conventional ultrasound system.

METHODS

A total of 21 healthy volunteers were recruited. Ultrasound was performed in two settings, using the robotic arm and conventional hand-held procedure. Images acquired were analyzed by separate radiologists.

RESULTS

Our study showed that the robotic arm model was feasible, and the results varied based on the organ imaged. The liver images showed no significant difference. For other organs, the need for repeat imaging was higher in the robotic arm, which could be attributed to the radiologist's learning curve and ability to control the haptic device. The doctor and volunteer surveys also showed significant comfort with acceptance of the technology and they expressed their desire to use it in the future.

CONCLUSION
This study shows that robotic ultrasound is feasible and is the need of the hour during the pandemic.

Key Words: Robotic ultrasound; Telemedicine; Ultrasonography; Haptic device; Pandemic

Core Tip: Robotic ultrasound aims to provide remote ultrasound access through a robotic system. This system allows the radiologist to manipulate the ultrasound probe remotely from a safe distant location, in a separate enclosure, thus ensuring the safety of the sonologist and negating the need for a personal protective equipment kit each time, especially in the current coronavirus pandemic. System setup in an intensive care unit (ICU) could ensure that the sonologist can perform the ultrasound without needing to enter the ICU. Going forward, a distance transmission system may also be potentially developed so that patients can also access care at a convenient location without the need to travel long distances, further breaking the chain of transmission. This can be invaluable in a setting where healthcare is not widely available, such as in underserved rural areas.

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INTRODUCTION

Severe acute respiratory syndrome coronavirus-2 has infected millions of people worldwide. As of May 2021, it has infected 157973438 people worldwide and the pandemic continues to rage with a tsunami of cases continuing to be reported in India, USA, and Brazil[1,2]. Healthcare workers (HCW) face an extremely high risk of infection for themselves, a risk that also gets transmitted to their families. Many healthcare workers have been infected and succumbed to the pandemic[3-6]. Although personal protective equipment (PPE) has been effective in protecting HCW, many countries grapple with shortages, and they have immensely added to plastic waste accumulation across the globe. Often, wearing PPE is not feasible or unavailable for HCW in non-coronavirus disease 2019 (COVID-19) designated areas, where the risk of transmission remains high in these times of the pandemic[7].

Telemedicine has evolved immensely in the last few years, though the adoption of these techniques was limited in the pre-pandemic era[8]. This was primarily due to the preference of many doctors and patients to personally see and converse traditionally[9]. The pandemic, however, has brought telemedicine and many of its applications to the forefront, proving that much of the care required can be guided from a distance. Adoption of this technology has received a boost with the pandemic as it provides the much-needed solution to address the challenge of protecting oneself while treating patients adequately.

Imaging plays a vital role in medicine at various stages in terms of diagnostic aid, aiding interventions, and procedures, and in the follow-up of patients. Ultrasonography is a non-invasive, non-ionizing, cost-effective, rapid, bedside, and easily available modality with immense use in point-of-care and follow-up examinations[10]. Often point-of-care ultrasound is the first modality with which a patient is assessed as he/she walks into the casualty. Ultrasound, however, requires an operator to be in close contact with a patient. Ultrasound rooms are often small and lack adequate ventilation, making the operator vulnerable to infection during the pandemic. In addition, ultrasound is often required in intensive care unit (ICU) settings. In the setting of COVID, they may be required for assessment of the chest or screening for thrombosis in veins. This often requires the operator to don and dough the PPE multiple times, despite needing to be present only for a limited amount of time.

Robotic ultrasound aims to provide remote ultrasound access through a robotic system. This system allows the radiologist to manipulate the ultrasound probe remotely from a safe distant location, in a separate enclosure, thus ensuring the safety of the sonologist and negating the need for a PPE kit each time. Similarly, such a system setup in an ICU could ensure that the sonologist can perform the ultrasound without needing to enter the ICU. Going forward, a distance transmission system may also be potentially developed so that patients can also access care at a convenient location without the need to travel long distances, further breaking the chain of transmission. This can be invaluable in a setting where healthcare is not widely available, such as in underserved rural areas.

In this study, we assessed one such system, where the robotic arm is mounted with the probe and is fixed next to the patient couch, and the sonologist operates it with a joystick, at some distance from the patient couch, with the two separated by a glass enclosure.

MATERIALS AND METHODS

This prospective study was conducted in the Department of Radio-diagnosis, Dr. BRA Institute Rotary Cancer Hospital, All India Institute of Medical Sciences, New Delhi, India between February 2021 and May 2021. Ethical approval was obtained from the institute ethics committee. Informed consent was obtained from all the volunteers. A total of 21 healthy volunteers were recruited. The sample size was one of convenience as this was a feasibility study. On each volunteer, ultrasound was performed in two settings, using the mobile robotic arm and the conventional hand-held ultrasound by the same sonologist, a few hours apart. The ultrasound examination was performed by a radiologist having 15 years of experience. The ultrasound images obtained using the mobile robotic arm and the conventional hand-held ultrasound were analyzed separately by another blinded radiologist having 20 years of experience. This study was performed to assess the feasibility of the model and its safety. All the healthy volunteers consenting to take part in the study were included. Volunteers who were < 18 years of age or those who did not give consent were excluded from the study.

Robotic ultrasound system setup

The robotic ultrasound system was co-developed by the Indian Institute of Technology, Delhi, and the All India Institute of Medical Sciences, New Delhi, in collaboration with Adverb Technologies. It consisted of a UR5e (by Universal Robots) robot arm at the patient site with the probe attached at its end using a custom-designed gripper. The doctor's site consisted of a geomatic haptic touch device (by 3D systems) used to operate the robotic arm. In addition to this haptic device, a monitor with a simple graphic user interface (GUI) was set up at the doctor's end to allow him or her to do basic control of the system. The sliding scale was provided on GUI to adjust the force exerted by the probe along with live camera feed to visualize the patient movements and responses. The systems were connected through a Wi-Fi router. Safety equipment was provided at both patient and doctor sites (Figure 1), such that the system would come to a complete standstill if pressed at either end.

Patient site

The patient site includes the robotic arm with the gripper, a USG machine, and an auxiliary staff person. The patient is made to lie on the table with its height and dimensions adjusted according to the robotic arm. The auxiliary staff applies a coupling agent (ultrasound jelly) onto the patient and positions the patient as required. The required transducer is fixed on the gripper based on the exam being performed. The patient is made to hold a safety switch to control.

In the current system, the auxiliary staff performed the ultrasound settings like gain depth and image labeling at the patient end. However, the staff may maintain a safe distance from the patient as they are not required to move the machine or position it continuously during the exam.

Doctor site

The doctor site includes the geomatic haptic device with a stylus tip that is held by the doctor and simulates the probe movements. It also provides haptic (sense of touch) feedback allowing the doctor to perceive feedback sensations of contact between the US probe and the patient body. It also has a user interface with a screen showing the ultrasound images and the patient. Since this was only a feasibility study, the doctor site was created on one end of the same room. This allows only the purpose of safe distancing to be fulfilled. However, this can evolve into a more sophisticated system by using a camera at the patient end to provide video feedback and sufficient bandwidth to prevent communication delays.

Ultrasound examination

The ultrasound machine used for the conventional and robotic ultrasound was the Sonosite M-TURBO model. Ultrasound images were acquired for each patient first using the robotic arm and subsequently by conventional hand-held ultrasound a few hours later. Time taken for each study was noted. After each study, the volunteer and the doctor were asked to fill out a satisfaction survey.

Image evaluation

All the images were transferred from the ultrasound machine to a USB drive. A google form questionnaire was created to analyze the images. Images were not annotated, and the conventional and robotic arm images were arranged randomly, each followed by the options.

The images acquired in both settings were evaluated by a reviewer with more than 10 years of experience in a blinded manner. All images were classified subjectively into either of the two groups:

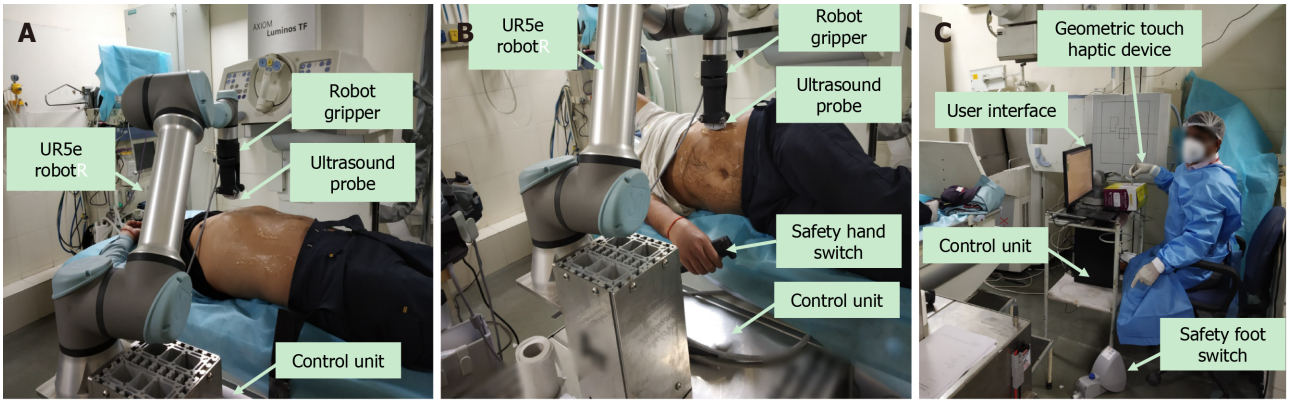

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Figure 1 Robotic ultrasound. A and B: Robotic ultrasound setup, which includes patient site; C: Doctor site.

Images adequate in resolution and for evaluation with some reservation, and those inadequate for evaluation needing repeat imaging. To compare the conventional hand-held ultrasound and robotic arm ultrasound image data, the Wilcoxon-signed rank test was used.

Satisfaction surveys

Feedback in the form of satisfaction surveys was taken from each volunteer and the radiologist after each ultrasound (Tables 1 and 2).

RESULTS

Demographics

All patients included in our study were males with a mean age of 37.09 ± 9.69 years. The average time taken to perform the conventional ultrasound was 4.05 min (range, 2-7 min), while that taken to perform an ultrasound using a robotic arm was 8.57 min (range, 4-17 min) (Table 3).

Ultrasound image evaluation

Images acquired using robotic arm ultrasound were divided into two groups (Figure 2). Image evaluation showed that 17/21 (80.9%) images of the liver were adequate with few reservations, while 4/21 (19%) required repeat imaging. Imaging of the gallbladder showed that 11/21 (52.4%) images were adequate, and 10/21 (47.6%) needed repeat imaging (Figure 3).

In the genito-urinary system, the right kidney (RK) image evaluation showed that 13/21 (61.9%) images were adequate with some reservations, and 8/21(38.1%) needed repeat imaging. For the left kidney (LK), 14/21 (66.67%) images were adequate with some reservations, and 7/21 (33.33%) needed repeat imaging. For the urinary bladder (UB), 11/21 (52.4%) images were adequate with some reservations, and 10/21 (47.6%) needed repeat imaging. Evaluation of the spleen ultrasound images showed that 13/21 (61.9%) images were adequate, and 8/21 (38.1%) needed repeat imaging.

Ultrasound images of the hepato-biliary system showed no significant difference in the need for repeat imaging of the liver between the conventional (2/21) and robotic arm (4/21) groups. GB evaluation showed a significant difference in the need for repeat imaging between the conventional (0/21) and robotic arm (10/21) groups.

In the genito-urinary system, there was a significant difference in the need for repeat imaging between the conventional (RK = 1/21, LK = 0/21, and UB = 2/21) and robotic arm (RK = 8/21, LK = 7/21, and UB = 10/21) ultrasound. Evaluation of the spleen also showed a significant difference in the need for repeat imaging in the conventional (1/21) and robotic arm (8/21) groups (Figure 4).

Doctor assessment

The radiologists performing the ultrasound using a robotic arm were asked to fill a satisfaction survey after each ultrasound examination. The radiologists somewhat disagreed with being able to use the system with ease in the initial five scans, followed by some agreement in being able to use the system easily in 15 scans. The radiologists somewhat agreed to understand the system in 18 scans. On the survey of wanting to use the robotic arm over a conventional system, the radiologist somewhat agreed in 13 scans. The radiologists reported difficulty in case of being able to handle errors with ease (somewhat disagreed in 11 cases). The radiologists showed some concern about the safety of the patients in seven scans. They found the user interface to be useful and trusted the results of the system

Table 1 Patient/volunteer satisfaction survey, *n* (%)

	Strongly disagree	Somewhat disagree	Neither disagree nor agree	Somewhat agree	Strongly agree
I was worried to undergo this procedure	0 (0)	7 (33.4)	2 (9.5)	12 (57.1)	0 (0)
I felt comfortable during the procedure	0 (0)	1 (4.8)	1 (4.8)	18 (85.6)	1 (4.8)
I felt no difference between this and conventional ultrasound	0 (0)	8 (38.1)	5 (23.8)	8 (38.1)	0 (0)
I felt comfortable knowing that doctor is controlling the robot	0 (0)	0 (0)	0 (0)	13 (61.9)	8 (38.1)
I will trust the results of this technology	0 (0)	5 (23.8)	6 (28.6)	10 (47.6)	0 (0)
I understand how the procedure took place	0 (0)	7 (33.4)	11 (52.4)	3 (14.3)	0 (0)
I felt less pressure on my body in comparison to conventional ultrasound	0 (0)	7 (33.33)	7 (33.33)	7 (33.33)	0 (0)
I would like to use this technology in future	0 (0)	2 (9.5)	4 (19.1)	12 (57.1)	3 (14.3)
I would recommend this technology to others	0 (0)	0 (0)	4 (19.1)	14 (66.6)	3 (14.3)
Overall rating					Average: 6.2

Table 2 Doctor satisfaction survey, *n* (%)

	Strongly disagree	Somewhat disagree	Neither disagree nor agree	Somewhat agree	Strongly agree
I could use the system easily	0 (0)	5 (23.8)	1 (4.8)	15 (71.4)	0 (0)
I have understanding of the working of the system	0 (0)	3 (14.3)	0 (0)	18 (85.7)	0 (0)
I could learn to use the system with more trials	0 (0)	0 (0)	0 (0)	8 (38.1)	13 (61.9)
I would like to use the system over conventional system	0 (0)	0 (0)	8(38.1)	13(61.9)	0 (0)
I feel the system is precise, safe, and effective	0 (0)	1 (4.8)	6 (28.6)	11 (52.4)	3 (14.2)
In case of errors, I was able to handle them with ease	0 (0)	11 (52.4)	4 (19)	6 (28.6)	0 (0)
I was not concerned about the safety of the patient during the procedure	0 (0)	7 (33.3)	0 (0)	13 (61.9)	1 (4.8)
I feel the user interface is useful	0 (0)	1 (4.8)	5 (23.8)	15 (71.4)	0 (0)
I trust the results of the system	0 (0)	0 (0)	4 (19.05)	13 (61.9)	4 (19.05)
Overall rating					Average: 6.38

in the majority of the cases. The overall rating of the system was between 5 and 7, with an average of 6.38 (Figure 5).

Volunteer assessment

Each volunteer was requested to fill out a satisfaction survey after the set of ultrasounds (both conventional and robotic arms).

The volunteers were somewhat worried to undergo this procedure (n = 12); however, most of them "somewhat agreed" to have felt comfortable during the procedure (n = 18). The volunteers "somewhat disagreed" to feeling no difference between robotic and conventional ultrasound. They somewhat agreed to be feeling more comfortable knowing that the doctor is controlling the robot. The volunteers were equivocal on trusting the results of the technology (n = 14 neither agreed nor disagreed, n = 4 somewhat agreed, and n = 1 somewhat disagreed). The volunteers somewhat agreed to understand how the procedure took place (n = 16). The volunteers did experience some pressure on their body with the robotic arm-loaded probe; however, they somewhat agreed (n = 19) that the pressure was equal to or less than conventional ultrasound and was not discomforting. The volunteers showed acceptance towards the technology (n = 12 somewhat agreed) and on their likelihood to use the technology in the future and recommended it to others (n = 14 somewhat agreed). The overall rating of the system was between 4 and 8, with an average of 6.2 (Figure 6). This can be attributed to the learning curve at the initial time.

Table 3 Time taken for performing ultrasound

Patient	Conventional hand-held (min)	Robotic arm (min)
1	3	17
2	5	17
3	5	17
4	3	15
6	2	10
7	4	9
8	4	8
9	7	6
10	4	9
11	4	6
12	5	5
13	6	8
14	3	8
15	4	6
16	3	5
17	4	4
18	5	4
19	3	7
20	5	6
21	3	8

DISCUSSION

There were only male volunteers in our study, which was coincidental and did not result from any deliberate selection or exclusion. The average time taken for ultrasound using a robotic arm in our study was almost double in comparison with that performed by hand-held ultrasound. Initial ultrasound exams in our study using the robotic arm took 17 min; however, as the operators became more accustomed to it, this was reduced to 4-7 min in the later ultrasound exams, which was comparable to that with handheld conventional ultrasound. This likely represents the learning curve associated with robotic ultrasound. This shows that with practice and as familiarity increases with the arm, imaging times would be very comparable to conventional ultrasound.

Image evaluation showed that most of the images acquired using the robotic arm were adequate with some reservations. In the evaluation of the liver, kidney, and spleen, the robotic arm performed well. However, evaluation of the gallbladder and UB showed that the robotic arm images needing repeat imaging were significantly more than conventional imaging. This could be attributed to fine probe angulations needed to focus on these organs.

In comparison with the conventional ultrasound images, evaluation of the liver using both modalities showed no significant difference. This could be attributed to the ability to image the liver in a supine manner without significant probe inclination. For the rest of the organs evaluated, there was a significant difference in the need for repeat imaging between conventional ultrasound and robotic arm ultrasound.

This can be attributed to the learning curve required for the radiologist to be able to control the haptic device and perform fine probe inclinations. With increasing experience later in the study, we observed that satisfactory scores for all images improved. The operators also subjectively reported better coordination and adaptation, which may help achieve better images using the robotic arm.

The radiologists performing the ultrasounds were able to use the system after an initial lag and understood the working of the system. The radiologists indicated their preference to use the system over the conventional ultrasound, which could be attributed partially to the current exposure of the healthcare workers during the pandemic. The radiologists experienced some difficulty in handling errors with the system, particularly at the beginning of the study, which needed the intervention of engineers. However, this was eventually addressed in the later part of the study, indicating again a need for dedicated training on the system before use. Regarding the safety of the patients, there was initial

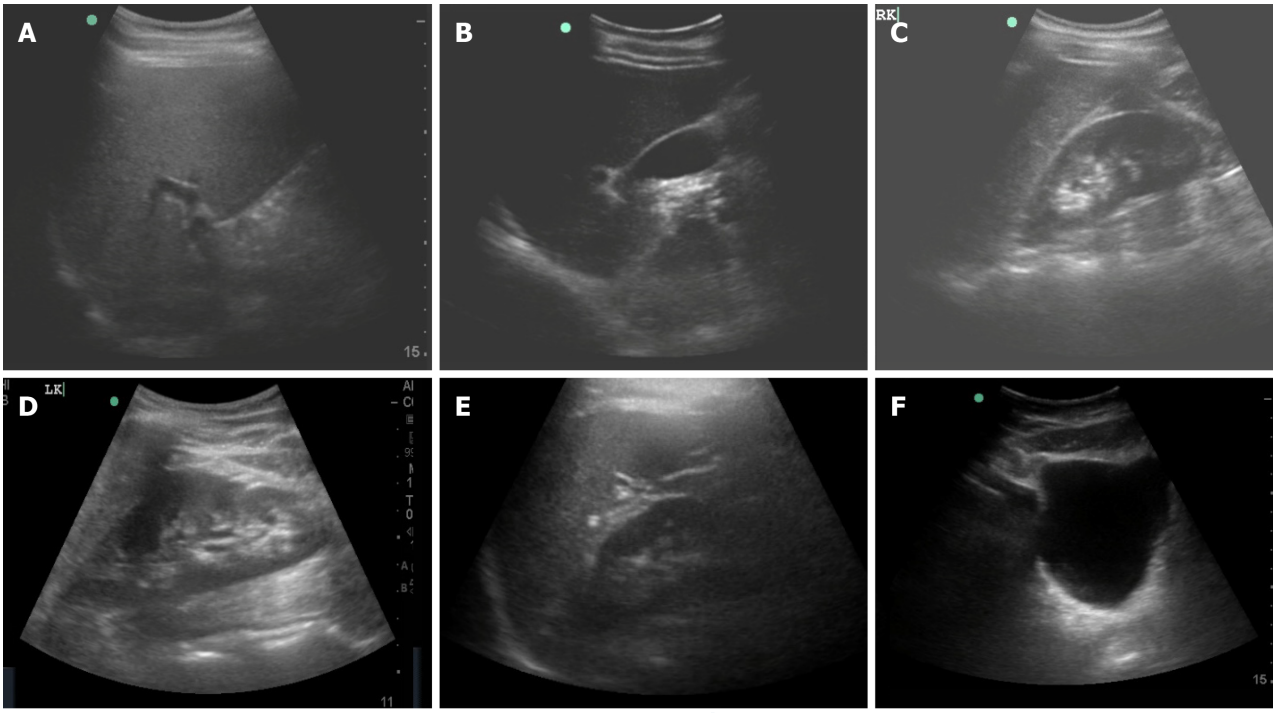

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Figure 2 Ultrasound images of abdominal organs acquired using a probe mounted on the robotic arm. A: Liver; B: Gall bladder; C: Right kidney; D: Left kidney; E: Spleen; F: Urinary bladder.

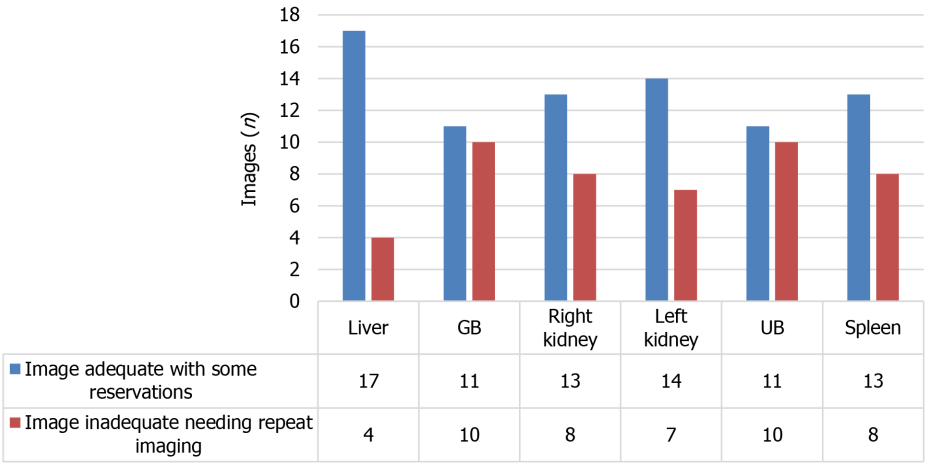

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Figure 3 Quality details of images acquired using robotic arm ultrasound. UB: Urinary bladder.

apprehension, both among radiologists and patients, concerning the landing of the robotic arm mounted with a probe on the patient's abdomen and the pressure exerted during the examination. However, assurance was provided about adequate prior testing; in addition, the interface at the doctor's end allowed force monitoring (through a slider on the computer screen) which may be used for dynamically increasing or decreasing the pressure whenever required. With controlled motions and increasing experience, the apprehension for patient safety was reduced. The radiologists found the user interface useful and were able to understand it with ease and trusted the results of the system. The radiologist performing the scan was more confident of the findings as he had scanned the entire organ compared to the single image provided for evaluation.

The volunteers were initially apprehensive to undergo the procedure as it was a first-time experience for them. Most of the volunteers were comfortable during the ultrasound. The volunteers felt that they were more comfortable with the conventional hand-held technique as it allowed more interaction with the radiologist. However, in some situations, they would be more comfortable using this technique. The awareness that the arm was being operated by a radiologist made them more comfortable and willing to

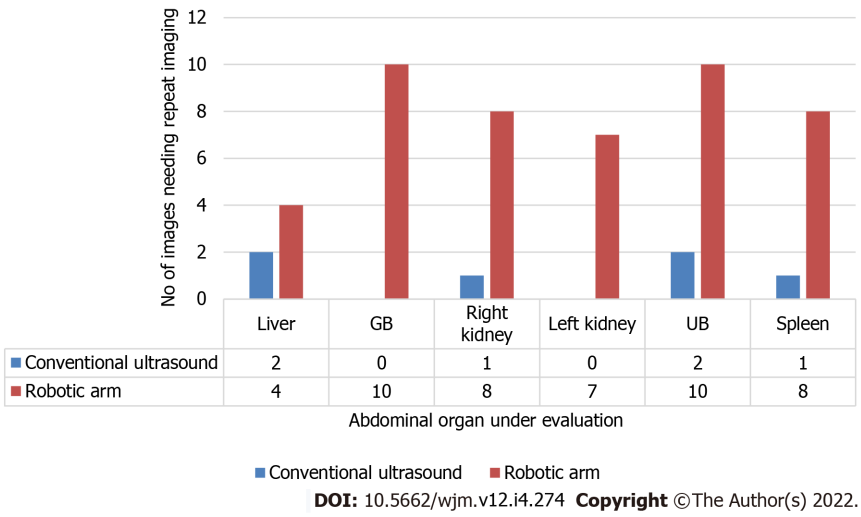

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Figure 4 Comparison between conventional and robotic ultrasound regarding the need for repeat imaging.

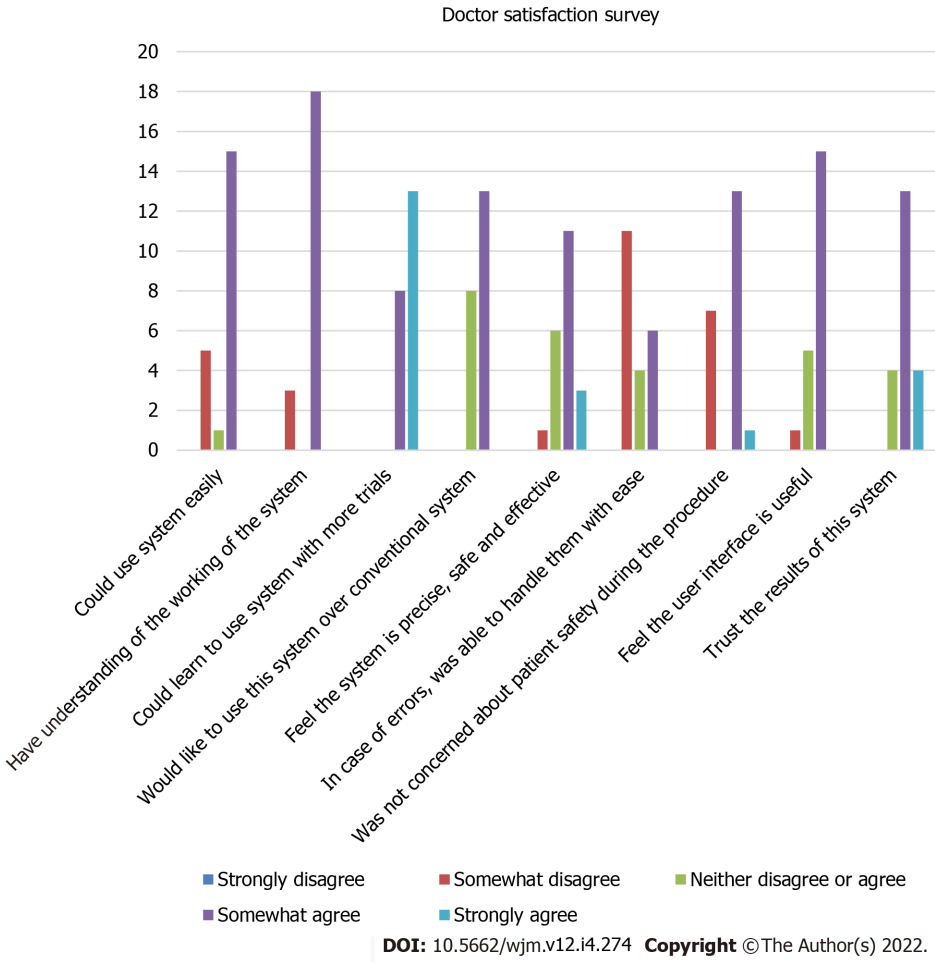

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Figure 5 Histogram showing results of the doctor satisfaction survey.

use the technology in the future. The volunteers believed that the force exerted by the robotic arm-mounted probe was almost similar to that exerted by conventional ultrasound. The volunteers also indicated that they felt secure and comfortable with the technology and were willing to use the same in the future and recommend it to others.

Limitations

The major limitation with the robotic arm is the increased setup and working cost. This cost is justified

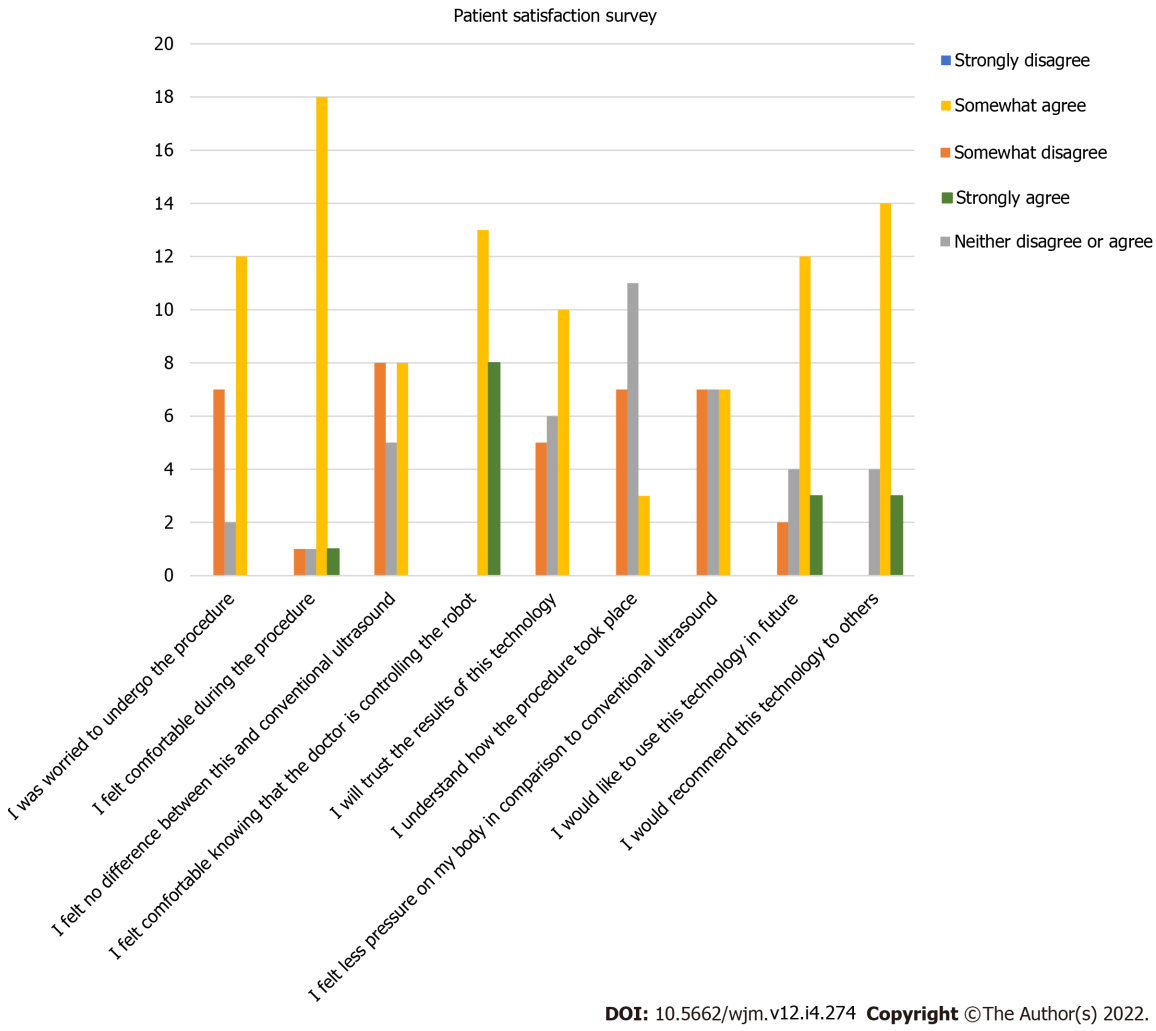

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Figure 6 Histogram showing results of the patient satisfaction survey.

in the case of pandemic situations like the current one. However, it may take some time to become a routine method of performing ultrasound.

With the current robotic system, auxiliary staff is needed at the patient end for helping with patient positioning and rotation during the examination and for the application of the coupling agent. However, the staff is not needed to remain close to the patient during the entire study and may maintain a safe distance once the patient is positioned and a coupling agent was applied. With the use of a robotic arm for gel application, this time may be further reduced.

There is a learning curve required to be able to operate the haptic device; however, it was seen that with adequate training, the initial difficulty could be mitigated. Time for comfortable ultrasound was also organ based with imaging requiring more probe angulation and inclination requiring more time for the operator to be able to coordinate the haptic device and the robotic arm's movements.

Our study had a small sample size, and recruiting more volunteers or patients would allow us to assess the system better.

CONCLUSION

Robotic ultrasound is the need of the hour, especially during this pandemic. The conventional hand-held ultrasound is the gold standard and is more cost-effective; however, in specific scenarios like the current pandemic, the robotic ultrasound is vital. Efficient use of this technology like other forms of telemedicine can help break the chain of transmission, reduce the amount of plastic waste, and provide adequate care while keeping the healthcare workers and patients safe. It will also play a role in broadening the reach of ultrasound in rural areas, thus improving the standards of health care.

ARTICLE HIGHLIGHTS

Research background

Special circumstances like the current pandemic have led to the need to exploit the utility of robotics and telecommunication systems to perform remote diagnostic ultrasound. It requires robust engineering effort to achieve high precision, flexibility, and repeatability, which can replace the conventional handheld ultrasound examination. A robotic ultrasound system was developed in this study so that ultrasound examination can be performed without having patient contact with the radiologist.

Research motivation

In the coronavirus 2019 (COVID-19) pandemic, the chances of cross-infection significantly increase among health care workers while performing ultrasound examination. There is a need to negate the need for a PPE kit each time when ultrasound examination is done, especially in COVID wards. This has motivated us to develop the robotic ultrasound system and conduct a study to validate it.

Research objectives

To perform ultrasound remotely using a mobile robotic arm on healthy volunteers to assess the feasibility and effectiveness of the system; validate the system by comparing the accuracy of the images generated through remote manipulations of probe attached to robotic arm by the radiologist; and to assess the comfort of the patient and radiologist with the robotic technology.

Research methods

This prospective study was conducted in the Department of Radio-diagnosis, All India Institute of Medical Sciences, New Delhi, India. Ethical approval was obtained from the institute ethics committee. Informed consent was taken from all the volunteers. A total of 21 healthy volunteers were recruited. On each volunteer, ultrasound was performed in two settings, using the mobile robotic arm and the conventional hand-held ultrasound by the same sonologist. The ultrasound images acquired using the mobile robotic arm and the conventional hand-held ultrasound were analyzed separately by another blinded radiologist.

Research results

Our study showed that the robotic arm model was safe and feasible, and the results varied based on the imaged abdominal organs. The liver images showed no significant difference. For other abdominal organs (such as the pancreas, spleen, kidneys, and urinary bladder), the need for repeat imaging was higher in case of robotic arm, which could be attributed to the learning curve and ability to control the haptic device. The doctor and volunteer surveys demonstrated significant comfort with acceptance of the technology and desire to use it in the future.

Research conclusions

This study shows that robotic ultrasound is safe and feasible and has potential to perform ultrasound with reliability.

Research perspectives

The scope of the developed tele-robotic ultrasound system can be expanded to perform ultrasound examinations remotely in distant rural places, emergency, trauma, and isolation wards.

FOOTNOTES

Author contributions: Chandrashekhara SH led the study in its conception, study design, statistical design, and manuscript writing and editing; all the authors have contributed in manuscript writing, study design and conduct, and statistical analysis.

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SYSTEMATIC REVIEWS

Telehealth has comparable outcomes to in-person diabetic foot care during the COVID-19 pandemic

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Abstract

BACKGROUND

The coronavirus disease 2019 (COVID-19) pandemic has posed obstacles to the delivery of diabetic foot care. In response to this remote healthcare services have been deployed offering monitoring, follow-up, and referral services to patients with diabetic foot ulcers and related conditions. Although, remote diabetic foot care has been studied before the COVID-19 pandemic as an alternative to in-person care, the peculiar situation of the pandemic, which dictates that remote care would be the sole available option for healthcare practitioners and patients, necessitates an evaluation of the relevant knowledge obtained since the beginning of the severe acute respiratory syndrome coronavirus 2 outbreak.

AIM

To perform a thorough search in PubMed/Medline and Cochrane to identify original records on the topic.

METHODS

To identify relevant peer-reviewed publications and gray literature, the authors searched PubMed-MEDLINE and Cochrane Library-Cochrane Central Register of Controlled Trials starting September 27 till October 31, 2021. The reference lists of the selected sources and relevant systematic reviews were also hand–searched to identify potentially relevant resources. Otherwise, the authors searched *Reference Citation Analysis* (https://www.referencecitationanalysis.com/).

RESULTS

A number of randomized prospective studies, case series, and case reports have shown that the effectiveness of remote care is comparable to in-person care in terms of hospitalizations, amputations, and mortality. The level of satisfaction of patients' receiving this type of care was high. The cost of remote healthcare was

not significantly lower than in - person care though.

CONCLUSION
It is noteworthy that remote care during the COVID-19 pandemic appeared to be more effective and well - received than remote care in the past. Nevertheless, larger studies spanning over longer time intervals are necessary in order to validate these results and provide additional insights.

Key Words: Diabetes; Diabetic foot; Telehealth; Telemedicine; COVID-19; SARS-CoV-2

Core Tip: Telehealth has a major potential to sustain and improve diabetic foot care during the coronavirus disease 2019 (COVID-19) pandemic. Studies reporting the experience of healthcare providers and patients around the globe are encouraging. These findings need to be validated with larger and long – term studies. In the post COVID era, the knowledge and experience obtained can serve as the standpoint of a hybrid approach of telemedicine and in-person care oriented towards delivering fast, efficient and cost-effective care to the patients.

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INTRODUCTION

During the coronavirus disease 2019 (COVID-19) pandemic, access to healthcare has been hampered by restrictions on citizen movement applied by governments globally as well as people in vulnerable demographics avoiding or delaying visiting healthcare facilities due to health concerns. Internal hospital rearrangements in order to prioritize COVID-19-centered care, especially relevant from our experience in the Diabetes Center of Tzaneio General Hospital of Piraeus in Greece, result in debilitation of the health systems' capacity to assess patients in need in a timely manner[1]. Patients with diabetes mellitus (DM) have been greatly affected by this. In addition to being a high-risk group, they need to consult their treating physicians often to maintain DM and its complications under control[2]. This need has remained unmet on many occasions. The repercussions of this have been evident particularly with regard to diabetic foot ulcerations, where lockdown periods have been followed by an increased rate of emergency hospitalizations and limb amputations[3].

Diabetic foot (DF), as defined by the International Working Group on the Diabetic Foot, is infection, ulceration or destruction of tissues of the foot associated with neuropathy and/or peripheral artery disease in the lower extremity of a person with (a history of) diabetes mellitus[4]. On a global scale, according to Global Burden of Disease an estimate of 131 million (1.8% of the population) people had developed a diabetes related lower extremity complication, chief among them being foot ulcers[5]. DF amounts for a significant amount of healthcare spending, as it is estimated to account for one third of diabetes spending which was $237 billion in 2017 in the United States, increasing by 26% from 2012[6, 7]. As a result, this is a disease which rivals cancer cost ($80.2B in 2015)[7]. We should also take into account indirect costs which include absenteeism from work or reduced productivity and even early mortality, which accounted for $90B[8].

While DF is one of the many diabetes sequelae, it is the one responsible for the most hospitalizations [5]. All diabetic patients have been estimated to have a 25% risk of developing a DF ulcer, with type 2 diabetics having a slightly higher chance[9,10]. Almost 50% of them are expected to become infected and in moderate to severe cases of infection about 20% will require to be amputated[11]. In fact, diabetes dominates nontraumatic lower extremity amputations, accounting for 85% of these operations.

To better understand the challenges of providing appropriate care and preventing amputations in patients with DF, one should consider this condition as a culmination of vascular disease, neuropathy and oftentimes disrupted immunity, vision impairment, debilitating comorbid conditions and frailty [12]. DF care requires frequent visualization, measurement and assessment of the wound by a specialist in addition to diverse treatment strategies including the use of medications, debridement patches and surgical cleaning of the wound. Having all this in mind, we can see how limited healthcare access directly affects the care of these individuals. The potential of remote care to patients unable to access healthcare facilities to stave off this highly morbid disease has been acknowledged before the pandemic. During the pandemic, the need to decrease the DF related burden of secondary and tertiary healthcare

facilities, prevent hospitalizations and protect the patients from life-changing complications became even more evident. Although there is abundant research about remote diabetes care before and during the pandemic, there is limited evidence focusing specifically on DF care under these circumstances.

The authors summarize primary research focusing on digital health and remote care for DF, its precipitating factors and sequelae and identify relevant research gaps and fields of action.

MATERIALS AND METHODS

To identify relevant peer-reviewed publications and gray literature, the authors searched PubMed-Medline and Cochrane Library-Cochrane Central Register of Controlled Trials starting September 27 till October 31, 2021. The reference lists of the selected sources and relevant systematic reviews were also hand–searched to identify potentially relevant resources. Otherwise, the authors searched *Reference Citation Analysis* (https://www.referencecitationanalysis.com/). The search terms: ("Digital health" OR "Remote Healthcare" OR "Telemedicine") AND ("Diabetic Foot"[MeSH] OR "Diabetic Angiopathies"[MeSH] OR "Foot Ulcer [MeSH]" OR "Diabetic Neuropathies"[MeSH]) AND "COVID-19"[MeSH] were used. Studies were included if they fulfilled all the following eligibility criteria: (1) Ongoing or published clinical studies reporting on digital and remote healthcare applications in the prevention or management of DF, its risk factors and sequelae; and (2) Epidemiological analyses and reports. A study was excluded if it met at least one of the following criteria: (1) Non-English publication language; and (2) Study types: editorials, opinion articles, perspectives, letters to the editor. No sample size restriction was applied when screening for eligible studies. Disputes in the selection of relevant studies were discussed between the two primary authors and a senior author until a consensus was reached. The literature was searched and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis extension for Scoping Reviews.

RESULTS

The initial search yielded 29 relevant publications, following the exclusion of non - primary sources from the database search and the deletion of duplicates. After screening titles and abstracts (n = 29) and excluding 12 records on the grounds of irrelevance to the topic, the full texts of 17 articles were assessed. Twelve studies were eventually included in the present review (Figure 1).

A detailed overview of the included studies' characteristics is presented in Table 1.

Eight clinical studies reported on the utilization of telehealth services during the COVID-19 pandemic in the United States, Europe, the United Kingdom, Turkey and India (2020-2021). Four clinical studies with similar design and outcomes that were conducted before the pandemic were included. These studies serve as control when compared to studies conducted during the COVID-19 pandemic. The majority of the studies presented observational data from cohorts, case series or sole case reports, fewer studies were designed as randomized clinical trials and one was based on a cross sectional survey. The existing evidence focused on the effectiveness of remote DF care and touched upon patients' experience and satisfaction and cost evaluation

Effectiveness of remote DF care

Studies regarding the effectiveness of various models of remote DF care during the COVID-19 pandemic paint a mostly positive picture. Utilizing a regime of virtual triage and consultations for a group of patients and comparing the outcomes with standard care from before the pandemic, Rastogi *et al*[13] concluded similar ulcer and limb outcomes in both groups, in a total of 1199 patients. In a randomized control trial (RCT) by Téot *et al*[14] in France that examined 173 patients, healing was insignificantly slower in the telehealth group, while both groups showed similar mortality rates. In an observational cohort study in Italy, Meloni *et al*[15] found telemedical care to be similarly as effective as outpatient care, while neutralizing healthcare setting transmission risk of COVID-19. Moving on to smaller scale studies, case report studies by Shankhdhar *et al*[16], Kavitha *et al*[17] and Ratliff *et al*[18], in India, India and United States respectively, report a positive healing outcome in an ulcer treated exclusively with telemedicine, effective assessment and follow-up of lower risk diabetic foot ulcer (DFU) cases and enhanced healing outcomes with telemedicine utilization respectively. Examining pre-pandemic literature on this topic we can derive that during recent years there has been a rise in interest in modernizing DFU care, although not without some potentially concerning findings. Interestingly studies before the pandemic report higher mortality in telehealth or inadequacy of remote care means like mobile photos - *e.g.*, Rasmussen *et al*[19]; van Netten *et al*[20]. In an RCT by Rasmussen *et al*[19] in 2015, comparing outpatient *vs* telemedical monitoring in DFU, similar healing and amputation rates were found in both groups of 401 patients, but with an inexplicable higher mortality rate in the second group. van Netten *et al*[20], while observing a cohort of 50 patients regarding the reliability of DFU ulcer using mobile phone images concluded it to be an unreliable method of remote assessment. Finally,

Table 1 Characteristics of the included studies

Ref.	Country	Study type	Objective of the study	Sample size	Key outcomes
Rastogi *et al* [13]	India, United Kingdom	Observational cohort	Virtual monitoring of DF complications during COVID-19	1199	Virtual healthcare has similar ulcer/limb outcomes as face-to-face care
Shankhdhar *et al*[16]	India	Case report	DF amputation prevention *via* telemedicine	1	Complete healing was achieved in 4 wk
Rasmussen *et al*[19]		Randomized controlled trial	Comparison between outpatient *vs* telemedical monitoring in DFU	401	Similar healing, amputation rates between both groups, higher mortality in telemedicine
Kilic *et al*[22]	Turkey	Randomized prospective	Developing and evaluating a mobile foot care application for persons with DM	88	Both groups increased knowledge (test group significantly more so), behavior, and self-efficacy
Téot *et al*[14]	France	Randomized Control Trial	Complex Wound Healing Outcomes for Outpatients Receiving Care *via* Telemedicine, Home Health, or Wound Clinic	173	Healing time marginally faster for in-person patients. Mortality comparable
Iacopi *et al* [23]	Italy	Survey	A survey on patients' perception of a telemedicine service for DF	206	Patients thought telemonitoring to be useful during and after the pandemic. Pts with complications worry more about DF than COVID-19
Kavitha *et al* [17]	India	Case Reports	Application of tele-podiatry in diabetic foot management	3	Telemedicine effective in low-risk cases of DFU and for referral of higher-risk. Also effective for follow up
Ratliff *et al* [18]	United States	Case Reports	Telehealth for Wound Management During the COVID-19 Pandemic	2	Improved healing outcomes with implemented telemedicine
Meloni *et al* [15]	Italy	Cohort	Management of DFU during COVID-19: Effectiveness of a new triage pathway	151	Effective telemedical care with negated hospital transmission
Fasterholdt *et al*[24]	Denmark	Randomized Control Trial	Cost-effectiveness of telemonitoring of diabetic foot ulcer patients	374	Telemedicine cost is €2039 less per patient treated *vs* standard care; not statistically significant. Amputation rates were similar
Smith-Strøm *et al*[21]	Norway	Cluster Randomized Control Trial	Effect of Telemedicine Follow-up Care on Diabetes-Related Foot Ulcers	182	No significant difference in healing time, deaths, number of consultations, or patient satisfaction between standard care *vs* telemedicine. TM group had significantly fewer amputations
van Netten *et al*[20]	Australia	Cohort	The validity and reliability of remote diabetic foot ulcer assessment using mobile phone images	50	Mobile phone images should not be used as a stand-alone diagnostic instrument for remote assessment of diabetic foot ulcers due to low reliability

DF: Diabetic foot; COVID-19: Coronavirus disease 2019; DFU: Diabetic foot ulcer.

standard medicine was found comparable to telemedicine in terms of outcome and patient satisfaction in a cluster RCT in Norway by Smith-Strøm *et al*[21], and notably, there were significantly less amputations in the telemedicine group.

Patients' perceptions and cost evaluation

As with any implementation in healthcare, it is of vital importance to gauge patient experience and perception. In a randomized pilot study in Turkey by Kilic *et al*[22], a novel mobile application was developed as a way for patients to submit their blood glucose measurements and potentially pictures as well. This was compared to receiving 30 min of training once by a healthcare professional. After 6 mo, patient education and behavior had improved, and overall increased self-efficacy was found. Patients reported, in their majority, that they appreciated this portal of communication with the specialists and overall thought this was an effective contribution to their DFU care. In another similar study by Iacopi *et al*[23] in Italy, 206 patients' opinions regarding their telemedicine consultations for DFU during the pandemic were assessed, as well as their anxiety regarding both COVID-19 and DFU. Patients were found to be very positive about their experience with telemedicine, finding it both very useful and a potential modality to keep using after the experiment. DFU patients seemed to be significantly more anxious regarding their existing DF disease compared to COVID-19, a result that was more apparent in the subgroup of patients with a history of ulceration, and even more prevalent in a subgroup that had undergone amputation. Regarding cost-effectiveness evaluation, in a study by Fasterholdt *et al*[24], the telemedical approach to treatment and monitoring of DFUs was not statistically significantly cheaper, although being cheaper by 2039 euros per patient. Some limitations of this study are the fact that it was

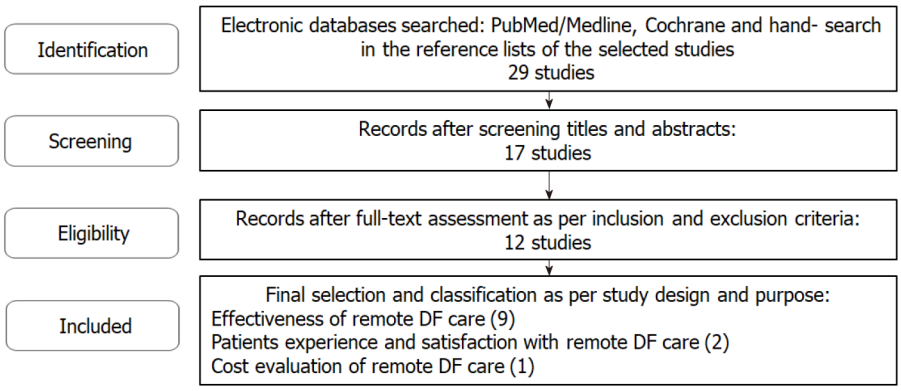

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Figure 1 Literature search flow diagram.

conducted in Denmark in a highly urban setting which reasonably translates to a smaller distance between the patient's setting and the care center in comparison to more rural areas. Furthermore, it did not take into account costs regarding personnel training and telemedicine implementation that would be required in order to apply this remote care modality.

Overall, available evidence suggests that remote DFU care has approximately similar or better outcomes to standard therapy regarding healing time and amputations. There is potential in utilizing telehealth methods in order to triage and consult patients without inconveniencing them with unnecessary and potentially hazardous trips to the physician's office. In the study from Rasmussen *et al* [19] it was concerning that mortality was statistically significantly higher in the telehealth group, but without a concrete accountable reason, more large-scale studies are needed to justify this result. Finally, patients seemed to be content with telehealth applications, can recognize their usefulness and would be open to adding a telehealth element to their treatment regime. It is unfortunate that evidence regarding patient satisfaction is scarce up to this point, but with a more patient-centered healthcare approach undertaken globally, it would be reasonable to expect additional literature in the upcoming years.

DISCUSSION

Overall, it appears that telehealth services for DF remote care during the COVID-19 pandemic have been described in a number of studies, primarily during the first months of 2020. Remote DF care had already been developed before the pandemic, but its use was limited. This can be linked to studies showing increased mortality among telehealth services recipients[19]. It seems that remote DF care during the COVID-19 pandemic became more effective than before, as shown in a study done in Australia examining the adherence to national DF guidelines and treatment efficacy using telemedicine [25]. This can be attributed to the accumulated knowledge that helped physicians to avoid mistakes of the past, to the increased familiarization of physicians, patients and caregivers with telehealth during the last two years and to the relatively short - term monitoring time of the studies in comparison with previous research. Perhaps, monitoring these patients for a longer time would still reveal adverse outcomes that have not become evident to date. This interpretation is subject to a number of factors.

Firstly, one should acknowledge the geographical variation scarcity of the literature. Studies that we reviewed come from Europe (Norway, Denmark, Italy, France, United Kingdom), United States, India and Turkey. Suffice it to say that there's a whole unknown world out there in terms of research on this subject, with large geographical regions not being represented as is. There is no literature regarding regions such as South America, Russia, Central Asia, Asia-Pacific and Africa, among others which inevitably lead to some level of bias. For example, the studies were done in countries and people that had access to remote healthcare services. This is best exemplified by the example of some developing countries, where it's estimated that about one third of the population has access to the internet, the principal foundation of telehealth in DFU. In addition, even in more developed countries there is often a shortage of tech-savvy physicians and lack of appropriate equipment. In our experience in public hospitals in Greece, for example, before the pandemic few web-cameras were available to use by the staff, a problem that thankfully was fixed on time.

There are certainly a number of knowledge gaps with regard to the matter. On top of those implied before. A considerable gap stems from the lack of cost effectiveness data in comparison to the pre-pandemic era. which necessitates further assessment, given that a non - cost effective model of remote care has lower likelihood to survive after the pandemic. Furthermore, there is no data in regard to the physician's perception of remote care, the level of physicians' digital literacy, accountability and financial compensation. Again, judging from the authors' experience, there is a lack of familiarity with

concurrent technology that's proportional to the personnel's age, mostly affecting the most senior members of the staff. In regards to the economics of telehealth, it is unclear whether state and private insurance have a homogenous stance of compensating remote care and whether they compensate at the same rate as in-person care, which, as expected, could stress medical staff. Last but not least, it is necessary to mention that the reported studies involved limited numbers of patients monitored for a number of weeks or months.

Future research needs to address the above limitations in the form of large scale and long-term studies providing - wherever necessary - head-to-head comparisons between patients treated in physical and remote settings. Studies evaluating patients and healthcare professionals' digital literacy can also help make digital health applications more relevant and improve the quality of the provided services. The latter calls for multidisciplinary research and initiatives involving digital health and network specialists apart from healthcare professionals, patients and caregivers.

CONCLUSION

Current evidence seems to favor the implementation of telehealth approaches to DF care. The encouraging results that have been reported thus far need to be monitored and reevaluated in the long term. Likewise, research needs to expand by getting more diverse and inclusive of a greater spectrum of socio-political landscapes. A good example of that is a recent study by Yunir *et al*[26] in Indonesia. We believe the conditions of the pandemic will inevitably contribute to the rapid development of the means of this method, either in the form of new software or patient and physician digital education and familiarization. This could serve as an excellent transition to the post-COVID era, as examined by Anichini *et al*[27], where a hybrid approach of telemedicine and in-person care will work best for all parties involved, delivering fast, efficient and cost-effective care to the patients.

ARTICLE HIGHLIGHTS

Research background

Diabetic foot (DF) care requires frequent visualization, measurement and assessment of the wound by a specialist in addition to diverse treatment modalities. Therefore, limited healthcare access directly affects the care of these individuals.

Research motivation

There is limited evidence focusing specifically on DF care during the pandemic.

Research objectives

To summarize the existing research focusing on digital health and remote care for DF, its precipitating factors and sequelae and identify relevant research gaps and fields of action.

Research methods

The authors searched studies published in PubMed-Medline and Cochrane Library-Cochrane Central Register of Controlled Trials from September 27 until October 31, 2021. The search terms: ("Digital health" OR "Remote Healthcare" OR "Telemedicine") AND ("Diabetic Foot"[MeSH] OR "Diabetic Angiopathies"[MeSH] OR "Foot Ulcer [MeSH]" OR "Diabetic Neuropathies"[MeSH]) AND "COVID-19"[MeSH] were used.

Research results

Remote diabetic foot ulcer care appears to be comparable to standard therapy in terms of outcomes, *i.e.*, healing time and amputation rates.

Research conclusions

The authors believe the conditions of the pandemic will inevitably contribute to the rapid development of the means of this method, either in the form of new software or patient and physician digital education and familiarization.

Research perspectives

These findings need to be validated with larger and long – term studies.

FOOTNOTES

Author contributions: Kamaratos-Sevdalis N co-performed literature search, performed the majority of the writing, and prepared the figures and tables; Kamaratos A and Papadakis M provided input in searching the literature and writing the paper; and Tsagkaris C designed the outline, co-performed literature search and coordinated the writing of the paper.

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SYSTEMATIC REVIEWS

Prevalence of precancerous lesions and conditions in India: A systematic review and meta-analysis

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Abstract

BACKGROUND

Smoking and chewing tobacco are associated with numerous oral mucosal lesions and conditions, often leading to cancer progression.

AIM

To investigate the prevalence of precancerous lesions and conditions among the Indian population.

METHODS

Systematic search was conducted for population or community-based observational epidemiological studies in PubMed, EMBASE, Web of Science, IndMED, Google Scholar, reports of the WHO South-East Asia Region, MOHFW India reports, Science Citation Index, WHO Index Medicus of the South-East Asian Region, *Reference Citation Analysis* (https://www.referencecitationanalysis.com/) and Open Grey from the earliest available up to 31st January 2022. The effect size was calculated for the prevalence of precancerous lesions and conditions.

RESULTS

One hundred sixty-two estimates from 130 studies yielded 52 high, 71 moderate, and seven low-quality studies from 823845. Point estimate based on cross-sectional studies for leukoplakia was 4.3% (95%CI: 4.0-4.6), oral submucous fibrosis was 2.7% (95%CI: 2.5-3.0), palatal lesions in reverse smokers and nicotine palatine were 5.8% (95%CI: 4.4-7.2), and Erythroplakia was 1.2% (95%CI: 0.7-1.7),

and lichen planus was 1.1% (95%CI: 0.9-1.2). Amongst hospital-based studies, the pooled prevalence for Leukoplakia was 6.7% (95%CI: 6.0-7.3), oral submucous fibrosis was 4.5% (95%CI: 4.2-4.9), lichen planus was 7.5% (95%CI: 5.3-9.6), and erythroplakia was 2.5% (95%CI: 0.4-4.5), and palatal lesions in reverse smokers and nicotine palatini were 11.5% (95%CI: 8.0-15.0).

CONCLUSION

Precancerous lesions and conditions are prevailing problems among the Indian population. It is mainly due to tobacco use, the smokeless form of tobacco. The meta-analysis indicates that hospital-based studies have a higher effect size of 6.7% than community-based studies. Patients who have already developed this condition may be advised to reduce their exposure to the risk factor to prevent the condition from progressing further.

Key Words: Prevalence; Pre-cancerous lesion; Pre-cancerous condition; India

Core Tip: World Health Organization assessment estimated that by 2020 tobacco-related death may exceed 1.5 million annually or 13% of all deaths in India. Tobacco consumption and smoking are seen in different socioeconomic groups, and this adverse habit is spread over urban and rural areas, giving rise to precancerous lesions and conditions. Prevalence of various oral lesions and conditions in India are varying in different studies. Numerous studies have been conducted throughout India to determine the prevalence of precancerous lesions and conditions.

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INTRODUCTION

World Health Organization (WHO) assessment estimated that by 2020 tobacco-related death may exceed 1.5 million annually, or 13% of all deaths in India[1]. Most smokers living in middle-income countries are the most giant smokers globally, amounting to 68% of all smokers[2]. South-East Asia Region (SEAR) is home to over 80% of global smokeless tobacco (SLT) users, higher than smoking[3]. Prevalence of tobacco use has decreased by 6%, points from 34.6% in GATS-1 in 2009-2010 to 28.6% in GATS-2 in 2016-2017 in India[4].

In the community-based study by Kvv *et al*[5] in 2004, 46579 were examined, and the prevalence of Lichen planus was 2.02%, and Leukoplakia was 1.73%. A study done by Mehrotra *et al*[6] in 2017 amongst 453823 people showed a prevalence of 1.29% for OSMF, 1% for Leukoplakia, and 0.47% for palatal lesions. In a hospital-based study done by Hazarey *et al*[7] in 2007, amongst 266418 patients prevalence of OSMF was 0.37%, and lichen planus was 0.7%. Erythroplakia 0.2% and Leukoplakia 4.8%. In a study done by Pratik *et al*[8] in 2015, amongst 10000 patients, the prevalence of Palatal lesions was 1.96%.

Tobacco consumption and smoking are seen in different socioeconomic groups, and this adverse habit is spread over urban and rural areas, giving rise to precancerous lesions and conditions. WHO has defined precancerous lesions as "a morphologically altered tissue in which oral cancer is more likely to occur than its normal counterpart"; a precancerous condition is 'a generalized state associated with a significantly increased cancer risk[9]. Leukoplakia associated with chewing habits may possess a greater chance of malignant transformation[10]. Different studies vary the prevalence of various oral lesions and conditions in India[11,12]. Numerous studies have been conducted throughout India to determine the prevalence of precancerous lesions and diseases. Hence, a pooled estimate was synthesized, which gave the prevalence of precancerous lesions and conditions among tobacco users.

MATERIALS AND METHODS

The title and details of this selected topic have been registered in PROSPERO (Reg. No. CRD42017062434). This systematic review was conducted according to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement[13].

Focused question

What is the prevalence of precancerous lesions and conditions among the Indian population?

Literature search

Two authors (Kumbhalwar A and Shetiya SH) independently carried out the literature search. Disagreements on study inclusion, quality assessment, and data extraction were resolved by deliberation or by the third author (Kakodkar P). We searched databases such as PubMed, EMBASE, Web of Science, IndMED, Google Scholar, reports of the WHO South-East Asia Region, CDC tobacco reports, MOHFW India reports, Science Citation Index, WHO Index Medicus of the South-East Asian Region, *Reference Citation Analysis* (https://www.referencecitationanalysis.com/) and Open Grey. The following keywords were utilized to search PubMed: "a precancerous lesion", "precancerous condition", "prevalence", and "India", various combinations of the keywords were used for each precancerous lesion and condition to search Google Scholar, and the first 50 pages were screened for relevant and non-duplicated articles.

Similarly, various combinations of the keywords were used in each of the databases, and the same process was repeated. A set of journals was identified based on their propensity to publish articles on this topic. Each journal issue's table of contents was then screened from the journal's inception till 31st January 2022 for relevant and non-duplicated articles. The cross-references of all selected papers were scanned for additional studies. Attempts were made to retrieve grey literature such as unpublished data, dissertations, and conference proceedings. To obtain publicly inaccessible data, a minimum of two email requests were sent to the corresponding author. If more than one article was published in a study, the article that provided the most updated data was selected.

Study selection

Population or community-based observational epidemiological studies were included. Hospital-based studies assessed oral health, precancerous lesions, and conditions due to risk factors like tobacco and alcohol. Epidemiological studies that provided inadequate information for calculating prevalence, prevalence mentioned in letters to the editor, short communication, and reviews were excluded. Studies that gave prevalence separately for smokers, chewers, and those with mixed habits were not included. Classification of precancerous lesions and conditions by WHO (1978)[14] was used for classifying lesions as leukoplakia, erythroplakia, palatal lesions in reverse smokers, and conditions as oral submucous fibrosis actinic keratosis, lichen planus, and discoid lupus erythematosus.

Data collection process

Data were extracted and calculated concerning the prevalence of the precancerous lesions and conditions from the various studies that met the inclusion criteria. Studies that gave a prevalence of white lesions were considered leukoplakia. Combined prevalence was taken for studies recording oral health status and treatment needs. The highest prevalence was considered for tobacco and alcohol users. The review's objective was to report the point estimate and pooled estimate of lesions and conditions. We carried out a qualitative and quantitative analysis of the observations.

Quality assessment

A total of 5 domains were assessed mainly, study characteristics (author, year of publication, study design) were collected, as well as population variables (sample size, gender, age, and related etiological factors), OPMD features (clinical diagnosis), and outcome measures (prevalence of OPMD). The maximum possible score was 8, and studies scoring 6-8 were classified as high quality, 3-5 as moderate, and less than or equal to 2 were categorized as low-quality studies. Two reviewers (Kumbhalwar A and Shetiya SH) independently conducted quality assessments with any disagreement resolved by consensus (Table 1).

Statistical analysis

The meta-analysis was performed using Open_Meta_Analyst software using the random effect method. We assumed that the estimates from various reviewed studies arose from different populations. The effect size of interest was the prevalence of the respective lesion and condition which developed. A given lesion/condition meta-analysis was conducted separately for community-based and hospital-based studies, and the pooled effect size was obtained. Sub-group analysis was performed to know the prevalence of lesion/condition before and after the Cigarette, and another Tobacco Product Act was implemented across various country regions (North, South, East, and West). Sixty-seven estimates were included from the North region, from South 170 estimates, from East 13 estimates, whereas 102 estimates were included in the review from the West region. Sensitivity analysis was also performed to know the prevalence amongst high, moderate, and low-quality studies. The community and hospital-based studies were pooled for the subgroup and sensitivity analysis. Heterogeneity was checked, and an I^2 value of > 50% was considered evidence of heterogeneity. Statistical significance was set at a P value < 0.05.

Table 1 Quality assessment

Domain	Criteria
Examination	0-Not mentioned
	1-Others (Nurse, ENT doctor, Medical officer, Health worker *etc.*)
	2-by dentist
Study settings	Community setting (field); Hospital setting.
Clinical examination	0-Not mentioned
	1-Visual screening (Tongue blade, Illumination)
	2-Mouth mirror
Sampling technique	Detailed description of the sampling strategy used, type of sampling (random or non-random) was determined.
	0-Not mentioned
	1-Non-random
	2-Random sampling
Sample size adequacy	If description of sample size calculations was not done, the relative precision was calculated (assuming simple random sampling) from the study sample size and estimated proportion.
	Relative precision was ≤ 20% of the point estimate
	0-Relative precision > 20% of the point estimate
	(*e.g.*, If the precision of a study varied from 8%-28% for different lesions and conditions in the mouth, prevalence of more than 20% was considered and score 0 was given)

RESULTS

Qualitative synthesis

A total of 493 unique records were screened by title and abstracts (Figure 1). After full-text reading, three papers were excluded. This exclusion resulted in 130 full-text studies (162 estimates) plus nine unpublished records, one record from National Oral Health Survey, India (2002-2003), and 27 studies from cross-references were included. Few studies were split into a, b, c, *etc.*, indicating the prevalence of lesion/condition within a study. For example, a. psychiatric and b. non-psychiatric inmates, a. fishermen, and b. non-fishermen *etc.* Actinic Keratosis and Discoid Lupus erythematosus considered in the review were not reported in any studies.

Age ranged from childhood to adulthood, and either gender and various states of India were considered. The prevalence of the precancerous lesions varied from 0.44%-73.8%, and the combined prevalence of oral precancerous lesions and conditions ranged from 2.79%-51.21%. One hundred sixty-two estimates from 130 community and hospital-based studies yielded 52 high, 71 moderate, and seven low-quality studies. Prevalence of lesions and conditions was estimated for various country regions, classified as North, South, East, and West.

Quantitative synthesis

A random-effect model was used for meta-analysis as the population from different states, age groups, and gender consuming varied types of smokeless tobacco and smoking were included. The point estimate for various lesions and conditions are given in Table 2.

Heterogeneity was high. Sub-group analysis provided effect size for multiple lesions and conditions before and after COTPA (2003) was enacted and different Indian regions. The studies published before 2003 showed a lower prevalence of the lesions and diseases than those carried out after 2003 (Table 3).

Prevalence of Lichen Planus was highest in the North region, whereas Leukoplakia, Erythroplakia, Palatal lesion, and Oral submucous fibrosis in the Western part of India (Table 4).

High-quality studies showed a higher prevalence of Erythroplakia, Palatal lesion in reverse smokers. OSMF except for Leukoplakia and lichen planus, seen in moderate quality studies (Table 5).

Pooled community and hospital-based studies, studies with high and moderate quality, and studies undertaken after COTPA was enacted showed similar effect sizes around 1.4%-1.6% (Figure 2). Meta-analysis showed an effect size between 8.1-9.2% amongst the moderate quality studies in the southern region, pooled studies, and after COTPA enactment (Figure 3A). Hospital-based studies, high-quality studies, and sand studies reflections from the western and northern parts showed larger effect sizes with wide confidence intervals (Figure 3B).

Table 2 Meta-Analyses for the point estimate of various pre-cancerous lesions and conditions

Precancerous lesions and conditions (Event/*n*)	No of estimates included	Point prevalence (95%CI)	*I*²(%)
LKP[1] (16828/901715)	92	4.3 (4.0-4.6)	99.47
LKP[2] (23090/653349)	46	6.7 (6.0-7.3)	99.74
LKP[3] (39918/1555064)	138	4.9 (4.7-5.2)	99.65
ERP[1] (223/20,164)	12	1.2 (0.7-1.7)	94.97
ERP[2] (1112/275674)	6	2.5 (0.4-4.5)	99.15
ERP[3] (1335/295838)	18	1.4 (1.0-1.7)	97.91
PL[1] (4353/488610)	16	5.8 (4.4-7.2)	99.49
PL[2] (8148/57951)	19	11.5 (8.0-15.0)	99.81
PL[3] (12501/546561)	35	8.9 (7.4-10.3)	99.77
OSMF[1] (9229/749768)	50	2.7 (2.5-3.0)	99.18
OSMF[2] (8160/487272)	38	4.5 (4.2-4.9)	99.58
OSMF[3] (17389/1237040)	88	3.4 (3.2-3.6)	99.43
LP[1] (2759/233782)	48	1.1 (0.9-1.2)	97.59
LP[2] (3811/50300)	25	7.5 (5.3-9.6)	99.92
LP[3] (6570/627947)	73	1.2 (1.1-1.3)	98.14

[1]Community-based studies.
[2]Hospital based studies.
[3]Pooled community and hospital based studies.
LKP: Leukoplakia; ERP: Erythroplakia; PL: Palatal lesion; OSMF: Oral Submucous fibrosis; LP: Lichen planus.

Table 3 Subgroup analyses of precancerous lesions and conditions showing pooled point prevalence before and after COTPA (2003) was enacted

Period of study	LKP (95%CI) (Estimates)	ERP (95%CI) (Estimates)	PL (95%CI) (Estimates)	OSMF (95%CI) (Estimates)	LP (95%CI) (Estimates)
≤ 2003	3.2 (2.5-4.0) (15)	No study; (0)	5.2 (-3.2-13.6); (2)	0.6 (0.4-0.7); (13)	0.6 (0.2-1.0); (4)
> 2003	5.5 (5.2-5.9); (123)	1.4 (1.0-1.7); (18)	9.2 (7.5-10.8); (33)	4.7 (4.4-5.0); (75)	1.3 (1.1-1.4); (69)

LKP: Leukoplakia; ERP: Erythroplakia; PL: Palatal lesion; OSMF: Oral Submucous fibrosis; LP: Lichen planus.

Table 4 Subgroup analyses of precancerous lesions and conditions showing pooled point prevalence in different regions of India

Regions	East (95%CI) (Estimates)	West (95%CI) (Estimates)	North (95%CI) (Estimates)	South (95%CI) (Estimates)
LKP	4.4 (1.9-6.9) (7)	8.4 (7.7-9.1) (44)	5.2 (4.6-5.8) (24)	3.4 (3.0-3.8) (63)
ERP	One study (1)	3.5 (2.1-5.0) (4)	2.9 (-1.5-7.2) (3)	1.0 (0.5-1.5) (10)
PL	No study (0)	16.9 (5.0-28.7) (5)	6.2 (2.4-10.0) (10)	8.1 (6.4-9.8) (20)
OSMF	3.4 (2.1-4.6) (2)	5.1 (4.7-5.4) (34)	1.4 (1.0-1.8) (15)	4.7 (4.2-5.3) (37)
LP	5.0 (1.2-8.7) (3)	1.2 (1.0-1.5) (15)	1.7 (1.2-2.3) (15)	1.0 (0.7-1.2) (40)

LKP: Leukoplakia; ERP: Erythroplakia; PL: Palatal lesion; OSMF: Oral Submucous fibrosis; LP: Lichen planus.

DISCUSSION

Summary of evidence

Most of the studies in the review were carried out in the Southern states of India. For those studies

Table 5 Sensitivity analyses of precancerous lesions and conditions showing pooled

Study quality (Studies)	LKP (95%CI)	ERP (95%CI)	PL (95%CI)	OSMF (95%CI)	LP (95%CI)
High (52)	4.6 (4.2-5.0)	1.6 (0.9-2.3)	11.0 (8.2-13.8)	4.0 (3.6-4.4)	1.1 (0.9-1.3)
Moderate (71)	6.6 (5.9-7.2)	1.6 (0.5-2.7)	8.2 (5.2-11.2)	3.3 (3.0-3.5)	1.3 (1.1-1.5)
Low (7)	1.4 (0.9-1.8)	One study	One study	2.8 (1.3-4.3)	No study

LKP: Leukoplakia; ERP: Erythroplakia; PL: Palatal lesion; OSMF: Oral Submucous fibrosis; LP: Lichen planus.

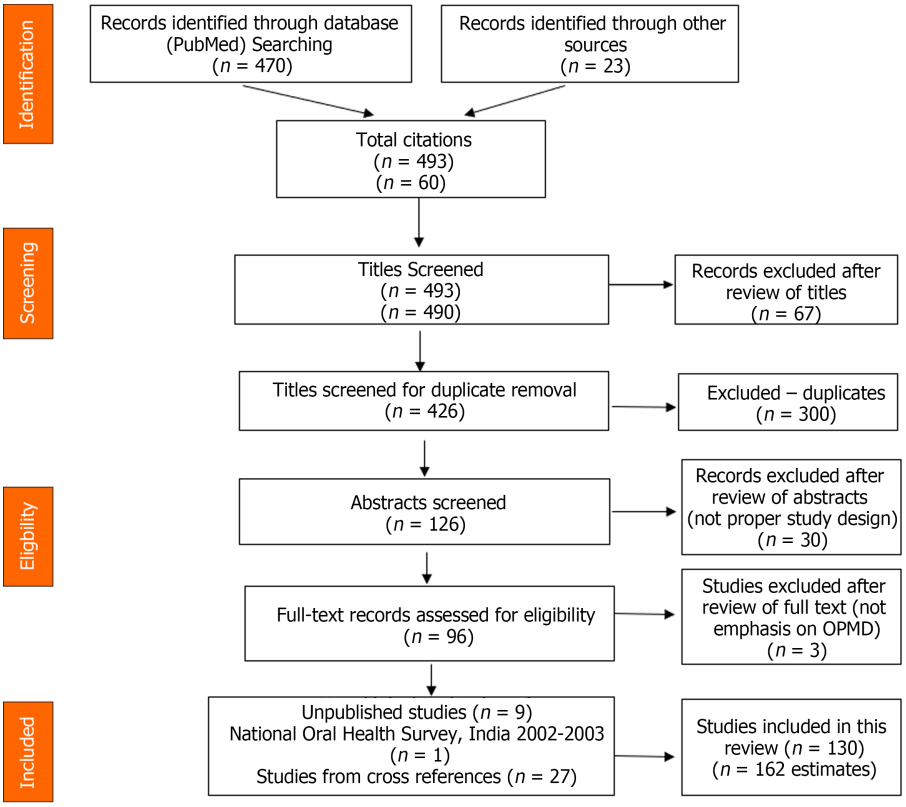

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Figure 1 Flow chart showing the literature searched.

where oral health assessment was the primary objective, the authors used WHO-Oral Health Assessment Proforma 1986, 1997, or 2013. Eighty-one field surveys were assessed, and 49 studies were exclusively done in the hospital setting, while most community and hospital-based studies were undertaken after 2003. Since there was no uniformity in the definition and classification of lesions and conditions, the chance of bias in determining the prevalence could be prevailing in the considered observational studies.

Prevalence of precancerous lesions and conditions in Population

More than 50% prevalence of all precancerous lesions and disorders was reported in specific population groups like fishermen and urban/rural populations who are tobacco consumers or slum dwellers or patients reporting to a dental college general population.

Leukoplakia

It was observed that the prevalence was higher amongst mine laborers, industrial workers, institutionalized elderly, chewers, jail inmates, fishermen, sex workers, tribes, and laborers in community-based studies. Most of the included studies have reported the prevalence of leukoplakia, unlike the other lesions and conditions.

Hospital-based studies, moderate quality records, and studies undertaken after COTPA was enacted showed a similar effect size of around 6%. Available estimates on the affordability of SLT products have indicated that they have become more affordable in India from 2001-to 2007[3]. However, the pooled estimate and the high-quality studies and those studies done in the northern region show an effect size

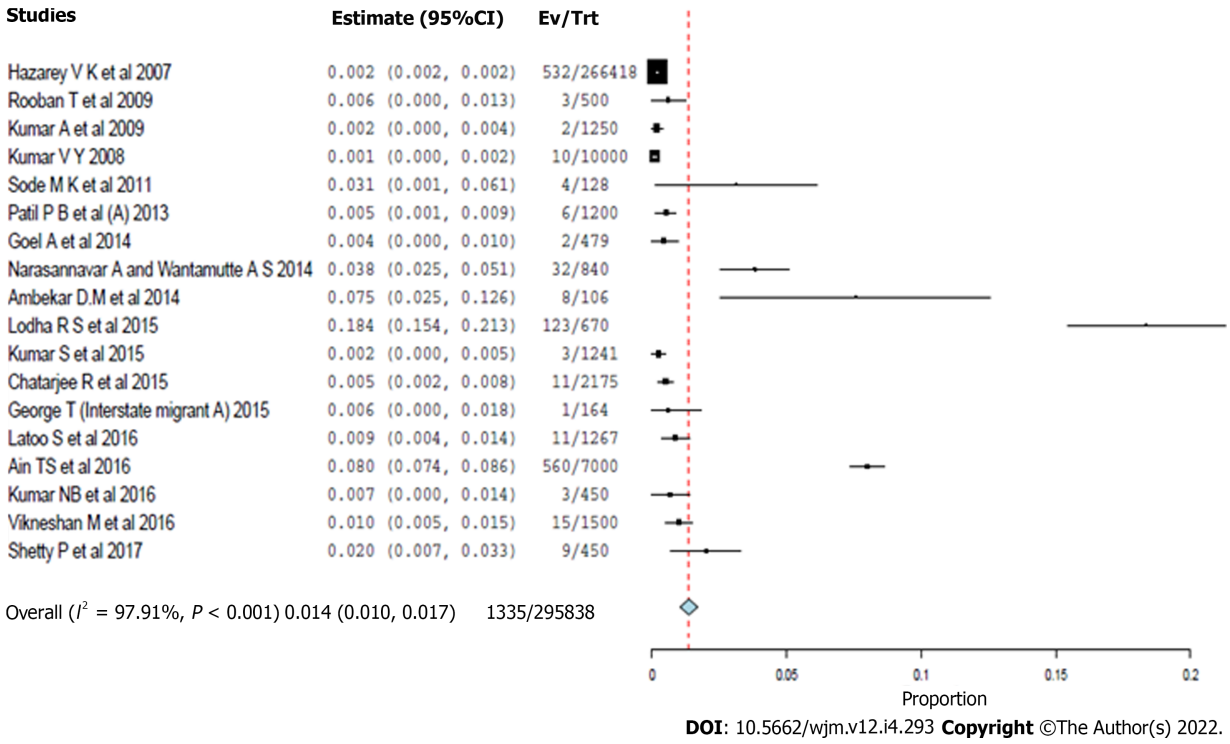

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Figure 2 Forest plot for the meta-analysis of erythroplakia prevalence (pooled community and hospital based studies).

of around 5%. This indicates that the prevalence of leukoplakia is around 5%-6%, and the effect sizes show a narrow confidence interval.

Hospital-based studies by Hazarey *et al*[7] and Kumar *et al*[15] conducted amongst 266418 and 25400 patients indicated a 4.8% and 6.16% prevalence for leukoplakia which is in concordance with this meta-analysis effect size. The risk factors that may cause oral leukoplakia include tobacco smoking (especially for localized leukoplakia), heavy alcohol consumption, and areca nut use. SLT lesions are caused by contact with tobacco-containing caustic agents. Early lesions are reversible and are usually resolved when the habit is discontinued. True leukoplakia has substantial potential to develop into cancer. It should be biopsied to rule out dysplasia[16]. Retail prices are generally lower for SLT products in low-income and low-middle-income countries and higher in high-income countries[3].

Erythroplakia

It was observed in the review that the prevalence of erythroplakia is higher in slum dwellers and prisoners. Erythroplakia showed an effect size of 1.2% for the community-based studies, which is lower than hospital-based studies. Pooled community and hospital-based studies, studies with high and moderate quality, and studies undertaken after COTPA was enacted showed similar effect sizes around 1.4%-1.6%. However, the western region's hospital-based studies estimates and analyses show an effect size of around 2.5%-3.4%. The prevalence of erythroplakia was about 1.4%-1.6%, as indicated by the narrow confidence interval. Studies carried out by Hazarey *et al*[7] and Kumar *et al*[15] amongst 266418 and 10000 study populations showed the prevalence of erythroplakia to be 0.2%-0.1% in concordance with the present meta-analysis effect size. Erythroplakia offers dysplastic features and often presents as "carcinoma in situ" at the time of biopsy. Heavy alcohol consumption and tobacco use are known to be important etiological factors[17,18]. Implementation of the ban on SLT Advertisement, Promotion, and Sponsorship status over high SLT burden Parties such as in India, is poor and exposure to SLT advertisements and promotion among adults is more elevated than smoked products[3], which is a deterrent to the cause of lesion and condition.

Lichen planus

The probable cause of lichen planus from the growing database of information about this disorder suggests specific immune responses, stress, and viral infection[19]. Though tobacco is not an etiological factor, it was part of the WHO classification and considered here. It was observed in the review that the prevalence is higher in the geriatric population. High and moderate-quality community-based studies in India's southern and western regions and those conducted after 2003 showed similar effect sizes with narrow confidence intervals. The prevalence of Lichen planus could be around 1%. Community-based studies done by Smith *et al*[20] and Kvv *et al*[5] amongst 57518 and 46579 people showed a prevalence of 0.63%-2.02%, which is in concordance with the present meta-analysis, which has indicated an effect size

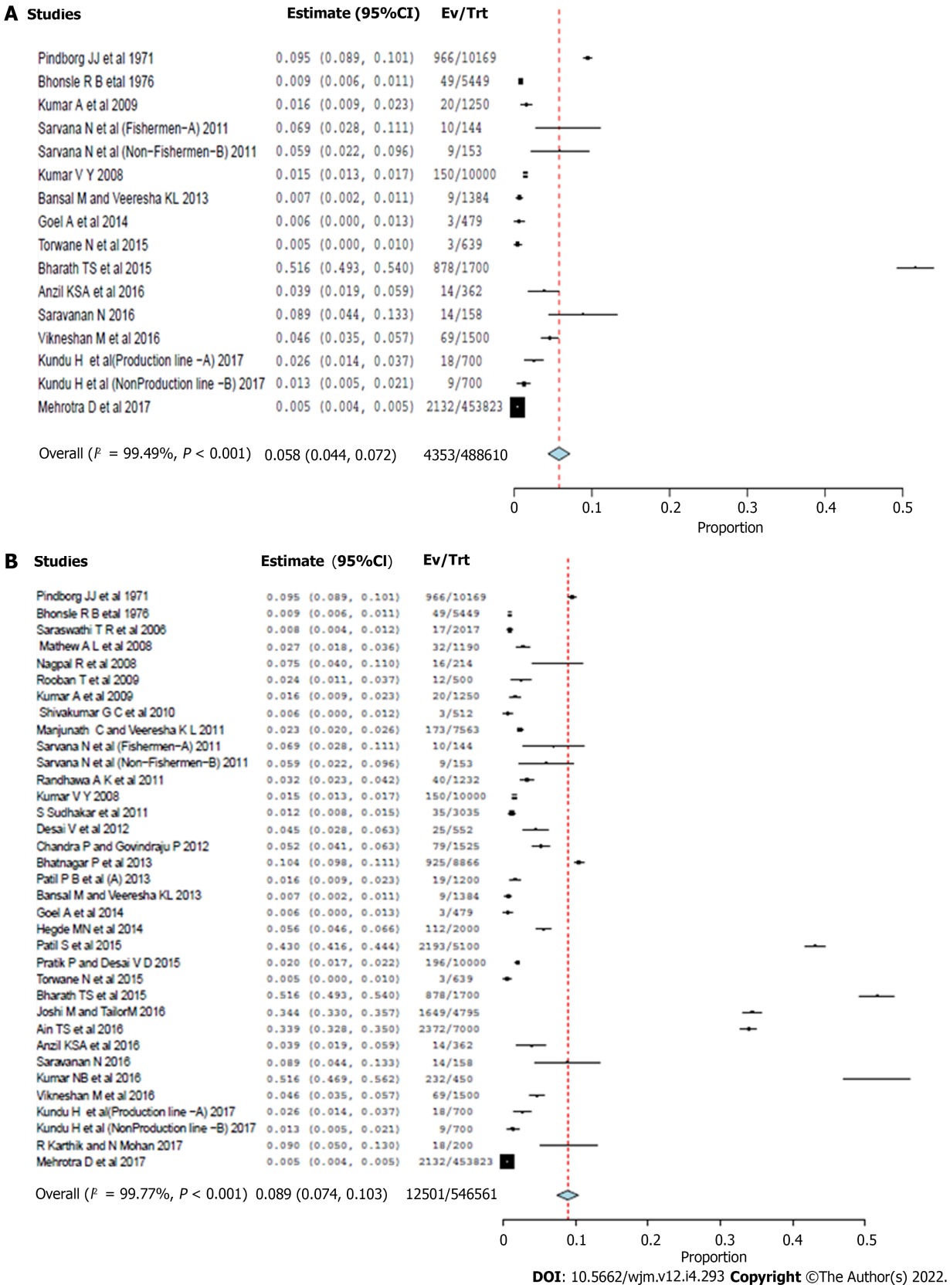

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Figure 3 Forest plot for the prevalence of palatal lesion in reverse smoker's. A: Community based studies; B: Pooled community and hospital-based studies.

of 1.1 %.

Oral submucous fibrosis

The review suggests that the prevalence is higher in jail inmates. Hospital-based studies, studies with

high quality, those done in India's southern and western region, and those undertaken after COTPA was enacted showed a similar effect size, around 4-5%, with a narrow confidence interval. Community-based studies, pooled studies, and studies with moderate quality showed a similar effect size of 3%. Studies were done by Kumar *et al*[15], and Mehrotra *et al*[6] amongst 25400 and 453823 study populations showed a prevalence of 1.29%, which is not in concordance with the present meta-analysis result, whereas 3.96%, which is in concordance with the current meta-analysis effect size. In southeast Asia, SLT is often mixed with areca nut, betel leaf, slaked lime, and spices, and these preparations are strongly associated with SMF, a fibrotic precancerous condition[21].

In India, some states and union territories have been relatively successful in enforcing the ban on gutkha. However, the tobacco industry is circumventing these bans by selling pan masala and tobacco in separate pouches. Successive GATS surveys in India in 2010 and 2017 revealed a significant reduction in the prevalence of SLT use in the general adult population[3]. As of 2016-2017, there has been a 1% reduction in the percentage of the adult population using *Gutkha* in India[4].

Palatal lesions in reverse smokers

This disorder is specific to populations who smoke with the lighted end of the cigarette inside the mouth, resulting in red, white, or mixed palate lesions[14]. Few studies reported palatal lesions in reverse smokers, showing a wide variation of prevalence from 0.9%[22]. 51.77%[23] from Goa and Andhra Pradesh amongst community-based studies. Fishers of Andhra Pradesh showed a higher prevalence. Meta-analysis showed an effect size between 8.1-9.2% amongst the moderate quality studies in the southern region, pooled studies, and after COTPA enactment. However, hospital-based studies, high-quality studies, and sand studies reflections from the western and northern parts showed larger effect sizes with wide confidence intervals. Studies were done by Mehrotra *et al*[6] and Pindborg *et al*[24] amongst 453823, and 10169 study populations showed a prevalence of 0.47%, which is not by the present meta-analysis result and 9.5%, which is in concordance with the current meta-analysis effect size.

Smoking prevalence in low and middle-income countries is projected to decline slower than in high-income countries[2]. There is a possibility of worldwide tuberculosis rates falling as much as 20% if smoking is eliminated[25]. 68% and 17% of cigarette and bidi smokers purchased loose cigarettes and bidis. On average, the expenditure incurred during the last purchase was Rs 30 and Rs 12.5, respectively, making the purchase easy for a commoner[4].

Actinic keratosis and discoid lupus erythematosus

Actinic keratosis represents a potentially malignant lip condition[26], while discoid lupus erythematosus (DLE) is a chronic autoimmune disease of unknown etiology[27]. None of the reviewed studies reported on the above two conditions.

CONCLUSION

Precancerous lesions and conditions are prevailing problems among the Indian population. It is mainly due to tobacco use, the smokeless form of tobacco. The meta-analysis indicates that hospital-based studies have a higher effect size of 6.7% than community-based studies, which show an effect size of 4.3%. Based on the present meta-analysis, the prevalence of leukoplakia is around 5%-6%. The majority of erythroplakia in community-based studies is lower (1.2%) than in hospital-based studies. The prevalence of erythroplakia in the current meta-analysis is 1.4-1.6%, as indicated by the narrow confidence interval. The prevalence of lichen planus seems to be higher (7.5%) for hospital-based studies than for community-based studies. The prevalence of Lichen planus is around 1%. The prevalence of oral submucous fibrosis seems higher (4.5%) for hospital-based studies than for community-based studies. The prevalence of oral submucous fibrosis was around 4%-5%. Compared to hospital-based studies, most Palatal lesions in community-based studies are lower (5.8%). Meta-analysis showed an effect size between 8.1%-9.2% amongst the moderate quality studies. Knowing these risk factors paved the way for more effective prevention of these pre-cancerous conditions. Patients who have already developed this condition may be advised to reduce their exposure to this risk factor to prevent the disorder from progressing further. Early intervention is essential to effective prevention. Thus, necessary efforts should be implemented.

ARTICLE HIGHLIGHTS

Research background

World Health Organization (WHO) assessment estimated that by 2020 tobacco-related death may exceed 1.5 million annually or 13% of all deaths in India. Tobacco consumption and smoking are seen in different socioeconomic groups, and this adverse habit is spread over urban and rural areas, giving rise

to precancerous lesions and conditions. Prevalence of various oral lesions and conditions in India are varying in different studies. Numerous studies have been conducted throughout India to determine the prevalence of precancerous lesions and conditions.

Research motivation

Tobacco consumption and smoking are seen in different socioeconomic groups, and this adverse habit is spread over urban and rural areas, giving rise to precancerous lesions and conditions. Different studies vary the prevalence of various oral lesions and conditions in India. So we were interested in compiling the data of precancerous lesions and conditions.

Research objectives

The objective of the present systematic literature review was to investigate a pooled estimate, which gave the prevalence of precancerous lesions and conditions among tobacco users in India population.

Research methods

Systematic search was conducted for population or community-based observational epidemiological studies in PubMed, EMBASE, Web of Science, IndMED, Google Scholar, reports of the WHO South-East Asia Region, MOHFW India reports, Science Citation Index, WHO Index Medicus of the South-East Asian Region, *Reference Citation Analysis* (https://www.referencecitationanalysis.com/) and Open Grey from the earliest available up to 31st January 2022. The effect size was calculated for the prevalence of precancerous lesions and conditions.

Research results

One hundred sixty-two estimates from 130 studies yielded 52 high, 71 moderate, and seven low-quality studies from 823845. Point estimate based on cross-sectional studies for leukoplakia was 4.3% (95%CI: 4.0-4.6), oral submucous fibrosis was 2.7% (95%CI: 2.5-3.0), palatal lesions in reverse smokers and nicotine palatine were 5.8% (95%CI: 4.4-7.2), and Erythroplakia was 1.2% (95%CI: 0.7-1.7), and lichen planus was 1.1% (95%CI: 0.9-1.2). Amongst hospital-based studies, the pooled prevalence for Leukoplakia was 6.7% (95%CI: 6.0-7.3), oral submucous fibrosis was 4.5% (95%CI: 4.2-4.9), lichen planus was 7.5% (95%CI: 5.3-9.6), and erythroplakia was 2.5% (95%CI: 0.4-4.5), and palatal lesions in reverse smokers and nicotine palatini were 11.5% (95%CI: 8.0-15.0). The meta-analysis indicates that hospital-based studies have a higher effect size of 6.7% than community-based studies, which show an effect size of 4.3%. Based on the present meta-analysis, the prevalence of leukoplakia is around 5%-6%. The prevalence of erythroplakia in community-based studies is lower (1.2%) than in hospital-based studies.

Research conclusions

Precancerous lesions and conditions are prevailing problems among the Indian population. It is mainly due to tobacco use, the smokeless form of tobacco. The meta-analysis indicates that hospital-based studies have a higher effect size of 6.7% than community-based studies. Patients who have already developed this condition may be advised to reduce their exposure to the risk factor to prevent the condition from progressing further.

Research perspectives

Knowing these risk factors paved the way for more effective prevention of these pre-cancerous conditions. Patients who have already developed this condition may be advised to reduce their exposure to this risk factor to prevent the disorder from progressing further. Early intervention is essential to effective prevention. Thus, necessary efforts should be implemented.

FOOTNOTES

Author contributions: Kumbhalwar A, Shetiya SH, Kakodkar P, Mehta V, Mathur A and Porwal P contributed to acquisition of data, analysis and interpretation of data, drafting the article, making critical revisions related to important intellectual content of the manuscript, and final approval; Mehta V contributed to acquisition of data, analysis and interpretation of data, making critical revisions related to important intellectual content of the manuscript, and final approval; Shetiya SH contributed to conception and design of the study, acquisition of data, making critical revisions related to important intellectual content of the manuscript, and final approval; and All authors discussed the results and contributed to the final manuscript.

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META-ANALYSIS

Prevalence of human leishmaniasis in Sudan: A systematic review and meta-analysis

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Abstract

BACKGROUND

There are three main forms of leishmaniasis in humans: cutaneous leishmaniasis (CL), visceral leishmaniasis (VL), and mucocutaneous leishmaniasis. The prevalence of human leishmaniasis varies widely in different countries and different regions of the same country. To date, there is no overall estimation of the prevalence of human leishmaniasis in Sudan.

AIM

To determine the pooled prevalence of human leishmaniasis and the disease risk factors among Sudanese citizens.

METHODS

From all articles written in English or Arabic languages conducted before the 4th of August 2021 from [Scopus, Web of Science, PubMed, and MEDLINE, African Journals Online (AJOL), ResearchGate, direct Google search, Google Scholar, and

universities websites], just 20 articles with a total of 230960 participants were eligible for this study. Data synthesis and analysis were done using STATA software, version 16. EndNote citation manager version X9.3.3 and *Reference Citation Analysis* (*RCA*) were used to remove the duplicated studies and manage the citation respectively.

RESULTS

The overall pooled prevalence of human leishmaniasis in Sudan was 21% (with confidence interval 12%-30%). CL was the most common type of leishmaniasis in Sudan, with a pooled prevalence of 26% followed by VL (18%). Nevertheless, the pooled prevalence of human leishmaniasis in Sudan was higher in males compared with females (60% *vs* 40%). The current results revealed that the people in the age group between 15 and 44 were the most affected group (60%), and central Sudan has the highest pooled prevalence of human leishmaniasis (27%) compared with other regions of Sudan. Finally, the prevalence of human leishmaniasis seems to decrease with time.

CONCLUSION

This study showed that human leishmaniasis infection is still endemic in many regions in Sudan and highly prevalent in central and eastern Sudan, and CL is the most prevalent in the country. Males and adults were more susceptible to infection compared with females and children. However, the human leishmaniasis prevalence decreased relatively over time.

Key Words: Cutaneous leishmaniasis; Human leishmaniasis; Meta-analysis; Prevalence; Sudan; Visceral leishmaniasis

Core Tip: A comprehensive systematic review and meta-analysis study was conducted to find the pooled prevalence of leishmaniasis and its associated factors among Sudanese citizens. After applying all required quality check-ups for the individual studies, 20 studies were included in this study. The pooled prevalence of human leishmaniasis in Sudan was 21%, and cutaneous leishmaniasis was the commonest form of leishmaniasis in Sudan. Finally, the results of this study showed that human leishmaniasis infection is still endemic in many regions in Sudan.

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INTRODUCTION

Neglected tropical zoonotic diseases (NTZDs) are endemic diseases in many developing countries of Africa, Asia, and Latin America[1]. The WHO's annual report for 2021, revealed that leishmaniasis is set among the top ten NTZDs worldwide[2].

In addition to the zoonotic nature of the disease, leishmaniasis is transmitted to humans by the infected female sandflies with *Leishmania* parasite, when it feeds on the human's blood[3]. There are three main forms of the disease in humans: cutaneous leishmaniasis (CL), which mainly features skin lesions, visceral leishmaniasis (VL), or Kala-azar, which can affect the spleen, liver, and bone marrow leading to some serious symptoms, and mucocutaneous leishmaniasis (ML)[3]. Of the three leishmaniasis forms, VL is the most lethal with a fatality rate of 95% if it is left untreated, while CL is the most common form[2]. In general, the high incidence and prevalence of human leishmaniasis have been highly associated with the prevalence of conditions that leads to a weak immune response, such as AIDS or tuberculosis. Studies also found a strong association between leishmaniasis prevalence and poor household status, poverty, population displacement, and recent climate change[4-7].

Evidence showed that the annual incidence of human leishmaniasis was 700000 to 1 million new cases. Although the disease was reported in 89 countries all around the world, East Africa, Southeast Asia, and South America countries, have the highest incidence rates[8]. Nevertheless, almost all reported outbreaks of human leishmaniasis were from East African countries, namely Sudan, South Sudan, and Ethiopia[9-13].

Sudan has a long history of leishmaniasis which was firstly discovered by Neave in the early 1900s [14]. Moreover, in the late twentieth century, several leishmaniasis (CL & VL) outbreaks were reported

in the eastern and central parts of the country[15]. The geographical distribution study of human leishmaniasis in Sudan found a high relationship between disease occurrence and vector distribution[16, 17]. Reports from Sudan found that the VL is endemic in the country, especially in the savannah area in the eastern and central parts of the country, which lies between four states (White Nile State in the west, Gadarif state in the east, Blue Nile State in the south, and Kassala state in the northeast)[18]. Moreover, VL was reported outside the savannah area in some scattered foci in the western parts of the country in Darfur states and Kordofan states[19]. Furthermore, national-wide epidemiological studies, report the endemic presence of the CL, especially in the northern, central, and western parts of the country[15]. For all the above reasons, it can be said that human leishmaniasis (both CL & VL) is endemic in Sudan, and the disease represents a serious health problem that affects the whole healthcare system[20].

Despite the importance of the disease in Sudan and the many published studies across the country that described the epidemiology of human leishmaniasis, no study estimated the overall prevalence of the disease at the national level exists to date. The lack of evidence about the disease in the country may prevent the health care policymakers and stakeholders from developing and adopting a suitable prevention program. Thus, the current study aimed to investigate the pooled prevalence of human leishmaniasis (both CL and VL) in Sudan.

MATERIALS AND METHODS

Eligibility criteria

The following were the eligibility criteria of this study: (1) All human observational studies; (2) Done on the Sudanese population; (3) Published in Arabic or English; (4) Reported the prevalence of human leishmaniasis (CL and VL); and (5) The positive cases of leishmaniasis were detected using the standards' diagnostics methods (serological and molecular tests). Moreover, studies were not eligible for this study (1) If they were reviews, letters, editorials, animal studies; and (2) If the full text was not available and has been requested from the author(s) through email but no feedback was received after 2 wk.

Information sources

This meta-analysis study was conducted according to the guideline of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[21]. The relevant information was retrieved from the electronic databases sources, namely Scopus, Web of Science, PubMed, MEDLINE, African Journals Online (AJOL), ResearchGate, direct Google search, Google Scholar, and universities websites. All indicated databases were searched from their inception to the 4th of August 2021, for human studies published in English and/or Arabic.

Search strategy

To achieve the current study objectives, a research strategy was developed using the Boolean search terms (AND, OR, NOT). The final search strategy included the use of Title/Abstract related to ((human leishmaniasis) AND ((prevalence) OR (epidemiology) OR (frequency)) OR (Risk factors)) AND Sudan) taken from the study questions. In addition, a manual search was done by the investigators for the grey literature and unpublished thesis/papers.

Selection process

Initially, primary screening was done based on the inclusion and exclusion criteria. Thereafter, all retrieved studies were exported to the EndNote citation manager version X9.3.3, to remove the duplicated studies. After that, the remaining articles were screened and evaluated by two investigators (Ahmed M and Abdulslam Abdullah A) independently. The investigators carefully have read the title, abstract, and full text of each article to eliminate the unrelated studies to prior defined objectives. Furthermore, the remaining articles were considered for further quality checkups against the checklist of Joanna Briggs Institute quality assessment tools[22]. Any discrepancy in the study findings was resolved by discussion between the two authors (Ahmed M and Abdulslam Abdullah A) or by consulting Hamad S. Figure 1 shows the selection process using the PRISMA statement flow diagram. Finally, *Reference Citation Analysis* (*RCA*) were used to manage the citation.

Data collection process

Following the selection process, the relevant data were extracted using a Microsoft word 2016 data extraction template.

Two investigators (Ahmed M and Abdulslam Abdullah A) contacted the corresponding author of any study that failed to report the information required for the eligibility criteria indicated above (*via* email) to get the original data; however, if the missing data were not obtained after 2 wk, a sensitivity analysis was carried out to remove the studies with the missing information. The extraction template contains (author/s name and publication year, study period, study design, study setting, geographical location

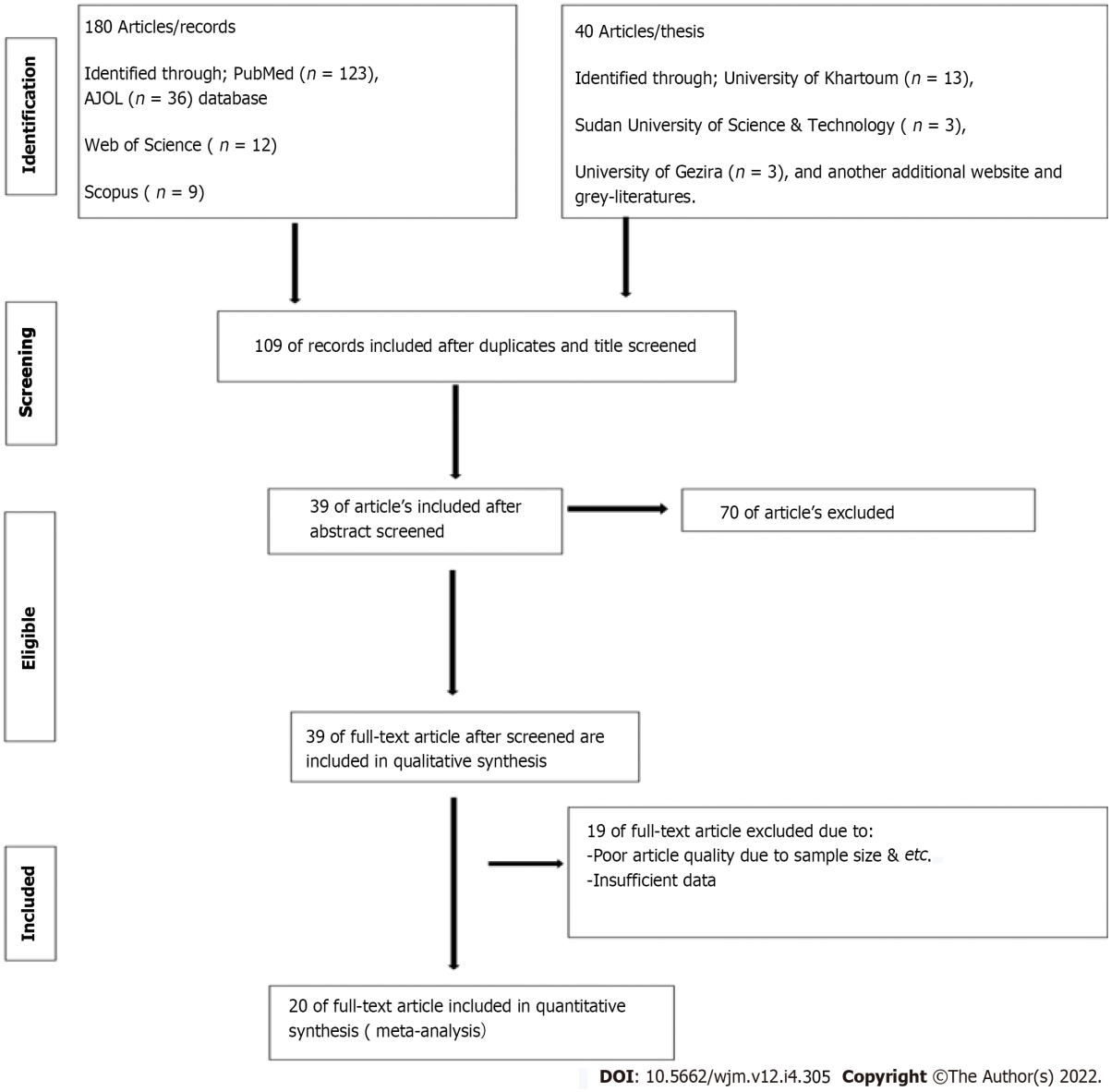

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Figure 1 Flow diagram of the studies included in this meta-analysis.

(based on state names), type of leishmaniasis (VL & CL), sample size, diagnostic method, and the prevalence of leishmaniasis in (overall and male and female) (Table 1). The accuracy of the data extraction process was verified by comparing the extraction results of 2 authors (Ahmed M and Abdulslam Abdullah A), who extracted the data independently, in a randomly- chosen set of papers (30% of the total).

Data items and effect measures

The prevalence of human leishmaniasis in Sudan was the main outcome of the current study. Moreover, the prevalence was measured from the individual studies by the direct report. To quantify the outcome, studies that reported the prevalence of VL and/or CL in their statistics were considered. Finally, the result was interpreted by the proportions of the population who tested positive for leishmaniasis compared with the total population studied.

Study risk of bias assessment

The risk of bias for this study was checked through several steps: firstly, by appraising the eligibility criteria for all retrieved articles by checking the title and abstract for each retrieved study; secondly, the full-text for each included study from step one was screened using the quality assessment criteria to identify their quality before the final selection. The quality assessment criteria used to determine if the study could be included were: (1) The presence of Leishman parasite in the patient was identified after performing the appropriate diagnostic tests; and (2) From the statistical point of view, the study sample was representative of the study population. To minimize the risk of bias two strategies were followed:

Table 1 Main characteristics of studies included in the meta-analysis

Ref.	Sample size	Method	Type of leishmaniasis	Geographical location	Study design	Study setting	Prevalence *n* (%)		
							Overall, *n* %	Male	Female
Hashim[24], 1997	126	PCR & LST	VL/CL	Central Sudan	CS	HB	43 (34.1)	NR	NR
El Dawi[25], 1994	44	DAT	VL	Central Sudan	PS	HB	19 (43.2)	NR	NR
Ibrahim[26], 2012	734	LST	CL	Central Sudan	CS	CB	73 (9.9)	NR	NR
Sharief *et al* [27], 2019	1781	DAT & LST	VL	Western Sudan	ES	CB	238 (13)	NR	NR
Osman[28], 2011	332	PCR	CL	Western Sudan	CS	CB	32 (9.6)	NR	NR
Noraldaim[29], 2012	110	DAT & ELISA	VL	Central Sudan	PS	CB	46 (41.8)	NR	NR
Mohamed *et al* [30], 2019	95	DAT	VL	Eastern Sudan	CS	CB	5 (5.3)	NR	NR
Dereure *et al* [31], 2003	79	Culture	VL	Eastern Sudan	NR	CB	23 (29.1)	NR	NR
EL-Safi *et al* [18], 2002	947	DAT & LST	VL	Eastern Sudan	CS	CB	132 (13.9)	NR	NR
El-Safi and Peters[32], 1991	9657	DAT	CL	Central Sudan	RS	HB	736 (7.6)	449 (61)	287 (39)
Atia[23], 2012	373	DAT	VL	Eastern Sudan	CS	CB	64 (17.2)	29 (45.3)	35 (54.7)
Abdallah[34], 2015	352	DAT & ELISA	VL	Eastern Sudan	PS	HB	71 (20.2)	43 (60.6)	28 (39.4)
Ebrahim[19], 2016	48972	Mixed	VL	Western Sudan	RS	HB	815 (1.7)	(62)	(38)
Awadalla[35], 2007	399	DAT	VL	Eastern Sudan	CS	CB	35 (8.8)	23 (65.7)	12 (34.3)
Muawyia *et al* [36], 2021	40	DAT	CL	Central Sudan	NR	HB	13 (32.5)	10 (76.9)	3 (23.1)
Osman *et al* [37], 2021	410	LST	CL	Northern Sudan	CS	CB	290 (70.7)	91 (31.4)	199 (68.6)
Abdullah *et al* [38], 2021	162443	Mixed	VL/CL	Western Sudan	RS	HB	7131 (4.4)	4657 (65.3)	2474 (34.7)
Ahmed[39], 2011	50	Mixed	VL	Central Sudan	CS	HB	NR	38 (76)	12 (24)
Ahmed[40], 2017	215	Mixed	VL	Eastern Sudan	R-CC	HB	NR	140 (65.1)	75 (34.9)
Collis *et al*[41], 2019	3801	LST	CL	Nationwide	RS	HB	NR	2178 (57.3)	1599 (42.1)

CB: Community-based study; CL: Cutaneous leishmaniasis; CS: Cross sectional study; DAT: Direct agglutination test; DS: Descriptive study; ELISA: Enzyme-linked immunosorbent assay; ES: Epidemiological surveys; HB: Hospital-based study; LST: Leishmania skin test; NR; Not reported; PCR: Polymerase chain reaction; PS: Prospective study; R-CC: Retrospective case-control study; RS: Retrospective study; VL: Visceral leishmaniasis.

(1) A comprehensive search for all electronic and non-electronic databases; and (2) A critical appraisal tool (Joanna Briggs Institute Quality Assessment Tool)[22] was used by two investigators (Ahmed M and Abdulslam Abdullah A) independently to critically appraise the included studies. The publication bias in the current review was checked primarily by Egger's regression test, which is a test of statistical symmetry of the funnel plot. Also, visualizing the inspection of the funnel plot was used to check the publication bias.

Registration and protocol

This review was developed based on the PRISMA guideline[21]. The review protocol has been registered by the International prospective register of systematic reviews at https://www.crd.york.ac.uk/Prospero/#recordDetails (No. CRD42021270418).

Synthesis methods

The collected study data were synthesized and analyzed using the STATA software, version 16.0 (Stata Corp LLC, 77845 Texas, United States). Statistically significance was set for *P* values < 0.05. The heterogeneity test was conducted using the degree of inconsistency (I^2), which is a percentage, and range from (0%-100%), moreover, Higgins *et al*[23] described the heterogeneity to be low, medium, and high, for the (I^2) values of 25%, 50%, and 75% respectively. Two statistical measurements were used to calculate the result of this study: effect size with a 95% confidence interval (CI) and standard error (SE). The prevalence of leishmaniasis (proportion) was considered as the effect size of this study, and the binomial distribution was used to calculate it.

The standard error was calculated using the following data: sample size (n) and the proportion of leishmaniasis positive case among the overall population (p) using the SE formula: SE = sqrt[]p (1-p) / n).

In the final meta-analysis model, the outcome of each individual study, as well as the pooled outcome of all included studies, were presented as forest plots [reported as effect size (prevalence) with a 95%CI]. The visual symmetry of the funnel plot and the result of Egger's Regression were used to check the potential publication bias; however, unlike other statistical tests reported here, the Egger's test was considered significant if the *P* values were less than 0.10.

A meta-regression test was conducted (univariate and multivariate regression) to investigate the possible relationship between study variables (study year/s, sample size, diagnostic method, type of leishmaniasis, study region, study design, and study setting) and the prevalence of human leishmaniasis. Sensitivity analysis and subgroup analysis were performed to check the potential heterogeneity among the included studies and possible sources of bias.

Finally, the findings of this study were reported according to the PRISMA guidelines[21], and the results were presented using a narrative synthesis and followed by the full meta-analysis chart.

RESULTS

Study selection

After applying the search strategies of the current study, a total of 220 articles were identified and retrieved from the major electronic databases sources. From the 220 retrieved articles, 111 of them were removed due to duplication. Meanwhile, the remaining 109 articles underwent further individual screening by title and abstract to appraise the eligibility criteria for each included study. Only 39 records were eligible for full-text quality assessment. Of the remaining 39 articles, 19 were excluded due to the article's poor quality and insufficient study data. Eventually, only 20 studies with good quality assessment scores that fulfilled the eligibility criteria were included in this review. Figure 1 showed the full process of study selection.

Study characteristics

As shown in Table 1, twenty studies with a total of 230960 participants, were included in the quantitative analysis. Of these 20 studies, 10 were community-based studies, and the remaining 10 studies were hospital-based. The overall prevalence of human leishmaniasis in Sudan was reported in 17 studies, and the association between sex and leishmaniasis was reported in 11 studies. Meanwhile, two types of human leishmaniasis were reported (CL & VL). The geographical distributions of included studies revealed that the most frequent study areas in the included studies were central and eastern Sudan (7 for each), followed by western Sudan (4), with only one study from northern Sudan, and no study from southern Sudan. From all available diagnostic tests for leishmania parasite, only five were mentioned in the included studies: (1) Direct agglutination test (DAT) - 11 times; (2) Leishmania skin test (LST) - 5 times; (3) Polymerase chain reaction (PCR) - 2 times; (4) Enzyme-linked immunosorbent assay test (ELISA) - 2 times; and (5) Culture method - 1 time.

Results of synthesis

The current comprehensive study found a wide range of human leishmaniasis prevalence in Sudan in the twenty included studies. The lowest prevalence of human leishmaniasis, 1.7 (95%CI: 1, 2.8) was reported in a study in North Darfur state[19], whereas, the highest prevalence, 70.7% (95%CI: 66, 75), was reported in a study done in Al-tragma Village, River Nile state[37]. From the included studies, the pooled prevalence of human leishmaniasis in Sudan was 21% (CI: 12%-30%), and the heterogeneity across studies was substantially high (with $P < 0.00001$; $I^2 = 98.9\%$); therefore, the random effect model (REML) was employed for the final analysis (Figure 2).

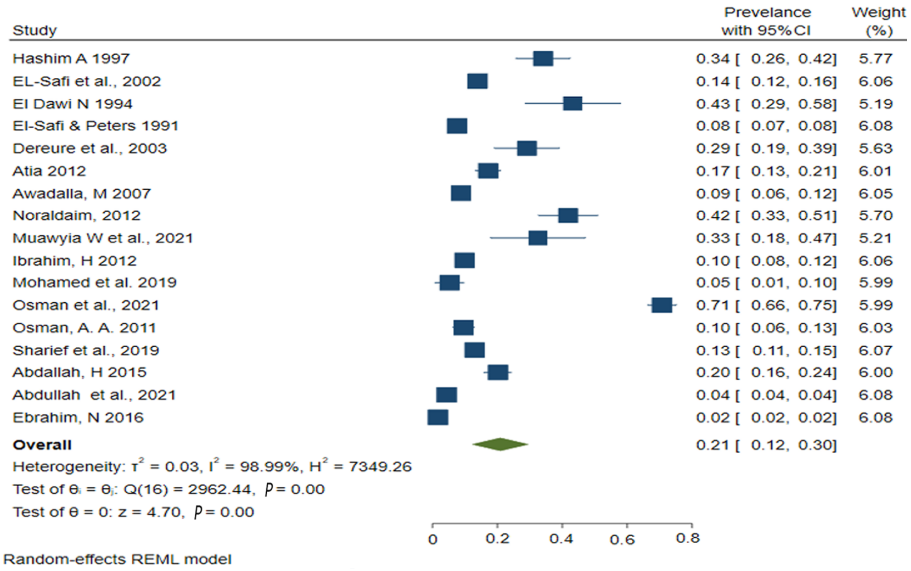

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Figure 2 Forest plot (random-effects model) for the pooled prevalence of human leishmaniasis in Sudan.

Meta-regression and sensitivity analysis

A meta-regression test was conducted (both univariate and multivariate regression) to investigate the possible relationship between study variables (study year/s, sample size, diagnostic method, type of leishmaniasis, study region, study design, and study setting) and the prevalence of human leishmaniasis. Nevertheless, all examined variables were not found to be statistically significant (Table 2), and from that, it can concluded that these study variables did not affect the heterogeneity. Alongside, the meta-regression, a sensitivity analysis was performed to identify the possible sources of the heterogeneity among the included studies. This study was done by sequentially excluding studies from the analysis model, but again the results did not find any significant difference in the analysis model. Thus, it can be concluded that the meta-analysis result of this study was stable. Furthermore, Egger's test for publication bias was statistically insignificant P = 0.128.

Subgroup analysis

Given the very high heterogeneity level presented in the analyses of human leishmaniasis, a subgroup analysis was done to find the effect of the sex, age, study year's, type of leishmaniasis, study region, study design, and study setting on the pooled prevalence of human leishmaniasis (Table 3). Using the above-mentioned factors as risk factors, the study results found that CL was the most common type of leishmaniasis in Sudan, with a pooled prevalence of 26% followed by combined infection (VL & CL) 19%, and then VL at 18%. Despite this, no data were found about ML prevalence in Sudan (Figure 3).

Nevertheless, the pooled prevalence of human leishmaniasis in Sudan was higher in males (60%) compared with females (40%) (Figure 4). In addition, the current results revealed that the people in the age group between 15 and 44 were the most affected group (60%) (Figure 5), central Sudan has the highest pooled prevalence of human leishmaniasis (27%) compared with other regions of Sudan, and the prevalence of human leishmaniasis seem to decrease over time (Table 3).

DISCUSSION

The United Nations Environment Programme 2020 annual report revealed that the majority of the Sudanese population live in the river Nile bank, forest zones, and savannah[42,43]. These areas are the natural areas for the presence of the carrier host (Sandfly)[17]. Also, the unique geographical location of Sudan, which is characterized by long staggered borders with some of leishmaniasis endemic areas on the southern and eastern sides of the country, together with the fact that the majority of the population are either nomad or farmers, make it very hard to control the disease in the country. Thus, human leishmaniasis poses an important challenge for the health and economic sectors in Sudan.

Based on a REML, the overall pooled prevalence of human leishmaniasis in Sudan was 21% (95%CI: 12%-30%). Assefa (2018), in Ethiopia, found almost the same result 21% (95%CI: 15%-27%)[44]. However, another Ethiopian study in 2021 found a lower result 9.13% (95%CI: 5-13.27)[45]. This difference between the two Ethiopian studies may be large because of the difference in the number of

Table 2 Heterogeneity related variables for the prevalence of human leishmaniasis in the current meta-analysis (based on meta regression)

Variables	Coefficient	SE	t	*P* > |t|	95%CI
Study yr/s	-0.0183371	0.0892299	-0.21	0.841	(-0.2171537, 0.1804794)
Sample size	-1.46e-06	1.10e-06	-1.33	0.204	(3.80e-06, 8.83e-07)
Diagnostic method	0.0152374	0.0500373	0.30	0.767	(-0.0962528, 0.1267275)
Type of leishmaniasis	-0.0271858	0.0653937	-0.42	0.686	(-0.172892, 0.1185204)
Study region	-0.0472426	0.0775729	-0.61	0.556	(-0.2200857, 0.1256005)
Study design	0.0029982	0.0584459	0.05	0.960	(-0.1272273, 0.1332237)
Study setting	-0.0381169	0.1762884	-0.22	0.833	(-0.4309118, 0.354678)

CI: Confidence interval.

Table 3 Subgroup analysis findings (random-effects model)

Analysis of leishmaniasis		Number of studies/pooled sample size	Pooled prevalence % (95%CI)	T^2	I^2%	H^2	*P* value
Sex	Male	10/13218	60 (52-67)	0.01	97.96	49.09	< 0.001
	Female	10/13218	40 (33-48)	0.01	97.96	49.07	< 0.001
Age group	< 5	5/8326	3 (1-6)	0.001	99.99	18316.61	< 0.001
	5-14	5/8326	22 (12-32)	0.01	97.76	44.50	< 0.001
	15-44	5/8326	60 (50-69)	0.01	95.53	22.38	< 0.001
	≥ 45	5/8326	14 (9-19)	0.001	92.09	12.63	< 0.001
Types of human leishmaniasis	VL	10/53152	18 (10-27)	0.02	99.28	138.39	< 0.001
	CL	5/11173	26 (2-50)	0.07	99.79	485.11	< 0.001
	VL/CL	2/162569	19 (10-48)	0.04	97.98	49.48	< 0.001
Study region	Central Sudan	6/10711	27 (14-40)	0.02	98.86	87.63	< 0.001
	Eastern Sudan	6/2245	15(9-21)	0.01	93.84	16.23	< 0.001
	Northern Sudan	1/410	71(66-75)	-	-	-	-
	Western Sudan	4/213528	7 (2-12)	0.00	99.97	2882.28	< 0.001
Study yr/s	Before 2000	5/10853	24 (12-37)	0.02	98.8	83.02	< 0.001
	Between 2001 to 2010	4/922	24 (9-39)	0.02	96.83	31.54	< 0.001
	After 2011	8/215119	17 (1-32)	0.05	100	24190.74	< 0.001
Study setting	Hospital-based study	8/221713	20 (10-31)	0.02	99.99	11092.03	< 0.001
	Community-based study	9/5181	21 (7-35)	0.05	99.54	218.75	< 0.001

I^2 index for the degree of heterogeneity; T^2 measure of heterogeneity; CI: Confidence interval; CL: Cutaneous leishmaniasis; VL: Visceral leishmaniasis.

included studies between them, which was 27 and 11, for Assefa[44], 2018, and Haftom *et al*[45], 2021, respectively. Although both Ethiopia and Sudan are endemic countries, the overall prevalence showed a clear discrepancy. The current findings showed variations in the pooled prevalence of human leishmaniasis between different geographical regions, age groups, sex, study settings, and years of publication, as well as between the different forms of human leishmaniasis. However, these findings showed no statistical difference in all subgroup analyses.

Two forms of human leishmaniasis were reported in Sudan, CL & VL, and between them, CL had the highest pooled prevalence of 26%, followed by mixed infection (CL & VL) (19%), and VL (18%). These results are in agreement with WHO findings[2] and Assefa's (2018) findings[44]. In contrast, Haftom and his colleagues (2021)[45] found a higher pooled prevalence of VL compared with CL in Ethiopia.

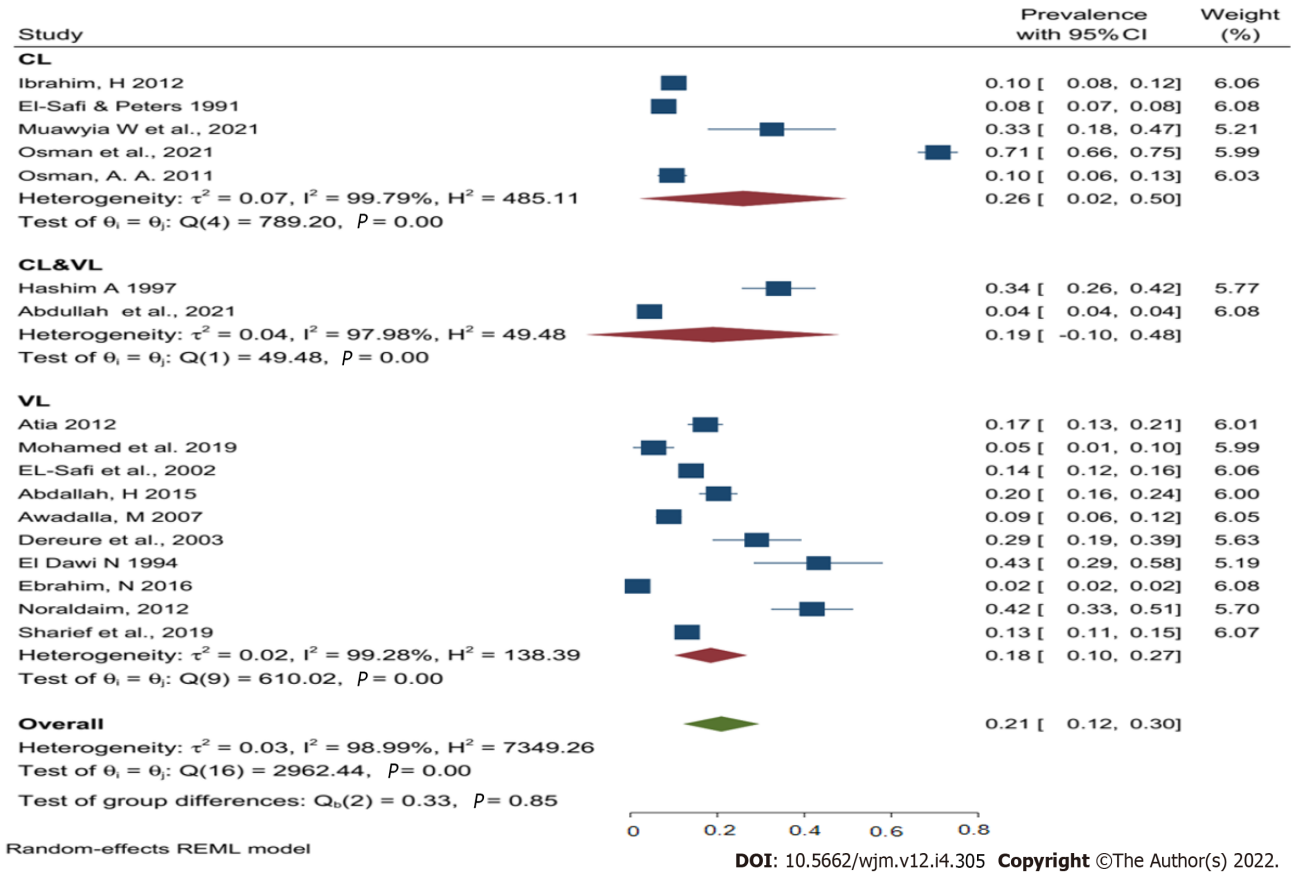

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Figure 3 Forest plot (random-effects model) for the pooled prevalence of the types of human leishmaniasis in Sudan.

Furthermore, the pooled prevalence of VL in Sudan was significantly higher than in Iran (2%)[46,47] and lower than it is in Latin America at 38.8%[48]. However, the current results seem to have one the highest reported pooled prevalence of CL worldwide, with only Sabzevari and his colleagues (2021)[49] in Iran reporting a higher pooled prevalence (45%); all other studies reported a lower pooled prevalence of CL compared with the current findings, including 22.1% in Mali[50], and 6.03%[45], and 19%[44] in Ethiopia.

The reported difference in the results between the other studies and this study may be due to differences in the climate of the study area, the study population, the absence of routine treatment or vaccinations for the definitive host, sample size, sampling procedure, and/or diagnostics method[51,52].

In Sudan usually, men work in agriculture and/or livestock sectors more than women and during the hot evenings and nights, men wear fewer clothes than women. These two main reasons may explain increased prevalence of leishmaniasis in Sudanese males compared with females (60% *vs* 40%), as these likely an increased risk of sand flies biting. These findings are in agreement with Haftom *et al*[45] (2021) in Ethiopia, Belo *et al*[53] (2013) in the Americas, and Kone *et al*[50] (2016) in Mali. However, two Iranian studies[47,49] disagreed with the current findings, with both studies reporting that the pooled prevalence of human leishmaniasis (CL & VL) was higher in females than in males. The sex-related difference in the pooled prevalence of human leishmaniasis between the current study and the Iranian studies may be due to differences in the cultural and work patterns between Sudan and Iran, Whereby, Iranian women were more involved in agricultural and livestock activities than men which would increase their risk of being bitten by sand flies[49,54].

The association between human leishmaniasis and age was reported in very few studies[26,32,35,37,38]; however, the pooled result reveals that people of workforce age had the highest pooled prevalence, followed by school-aged children and the infants. This makes sense because people who work in the agriculture and/or livestock sectors are at a higher risk of being bitten by sand flies. Similar results were found in Iran[47,49], Mali[50], and the Americas[53].

This meta-analysis study found that central Sudan has the highest reported pooled prevalence of human leishmaniasis compared with other parts of the country, and, generally, the pooled prevalence of human leishmaniasis in Sudan was decreasing over time. This result is corresponding with Al-Salem *et al*[6] (2016), who stated that "between 1985 and 2005, many epidemics of VL and CL were reported in Sudan, especially in central Sudan", and resulting from that, a high overall prevalence of human leishmaniasis in the same period of time in central Sudan. The relatively high prevalence of human leishmaniasis in Sudan may be due to the negative effects of the Sudanese civil war. Consequently, the

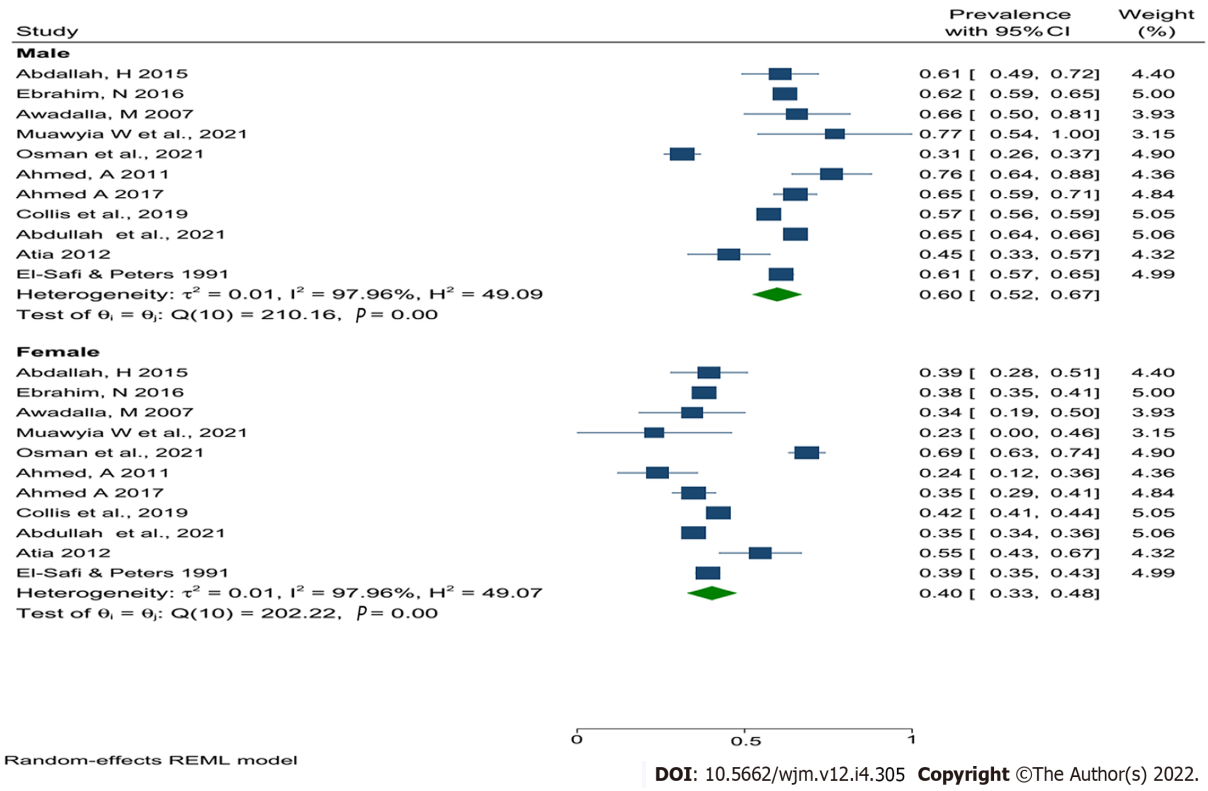

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Figure 4 Forest plot (random-effects model) for the pooled prevalence of human leishmaniasis in males and females in Sudan.

overall prevalence of human leishmaniasis and VL were significantly decreased after the leaders of the two war parties [The federal government of Sudan and the Sudan People's Liberation Army (SPLA)] signed the Comprehensive Peace Agreement on January 9, 2005 to stop the ongoing civil war[55].

Despite the seriousness of human leishmaniasis in Sudan, as presented in the current comprehensive study, no data is available about the economic impact of the disease on the livestock sector and public health sector in the country; thus, work needs to be done to cover the gap in this area. In addition, in our humble opinion, a collaborative effort and immediate action need to be taken from the policymakers and governments (federal and state government), to adopt a national wide epidemiological program to clarify the design of regional strategies and to guide the development of prevention and eradication programs in light of the one health concept during and beyond the COVID-19 pandemic.

The strengths of this study were the use of comprehensive search strategies to ensure that all published and unpublished studies related to the study objectives were included, and the use of standardized quality tools to evaluate the quality of the included studies. Finally, studies with abstracts were only included in this study.

The absence of data about patient places of residence, Leishman parasite species, and other potential risk factors in some included studies, are considered as limitations of the current study.

To the best of our knowledge, the current study is the first systematic review and meta-analysis study regarding the epidemiology of leishmaniasis in Sudanese citizens. Unluckily, there are very few published meta-analysis studies on the overall prevalence of human leishmaniasis, particularly in developing countries to compare with.

CONCLUSION

This systematic review and meta-analysis showed that human leishmaniasis infection is still endemic in many regions in Sudan and highly prevalent in central and eastern Sudan, and cutaneous leishmaniasis is the most prevalent in Sudan. Males and adults were more susceptible to infection compared with females and children. However, the human leishmaniasis prevalence decreased relatively over time. The presence of the high heterogeneity among the included studies should be considered when interpreting this study's findings. There is a lack of published research about human leishmaniasis in northern and southern regions Sudan. Research need to be updated and more research needs to be conducted in many regions in Sudan to provide adequate information.

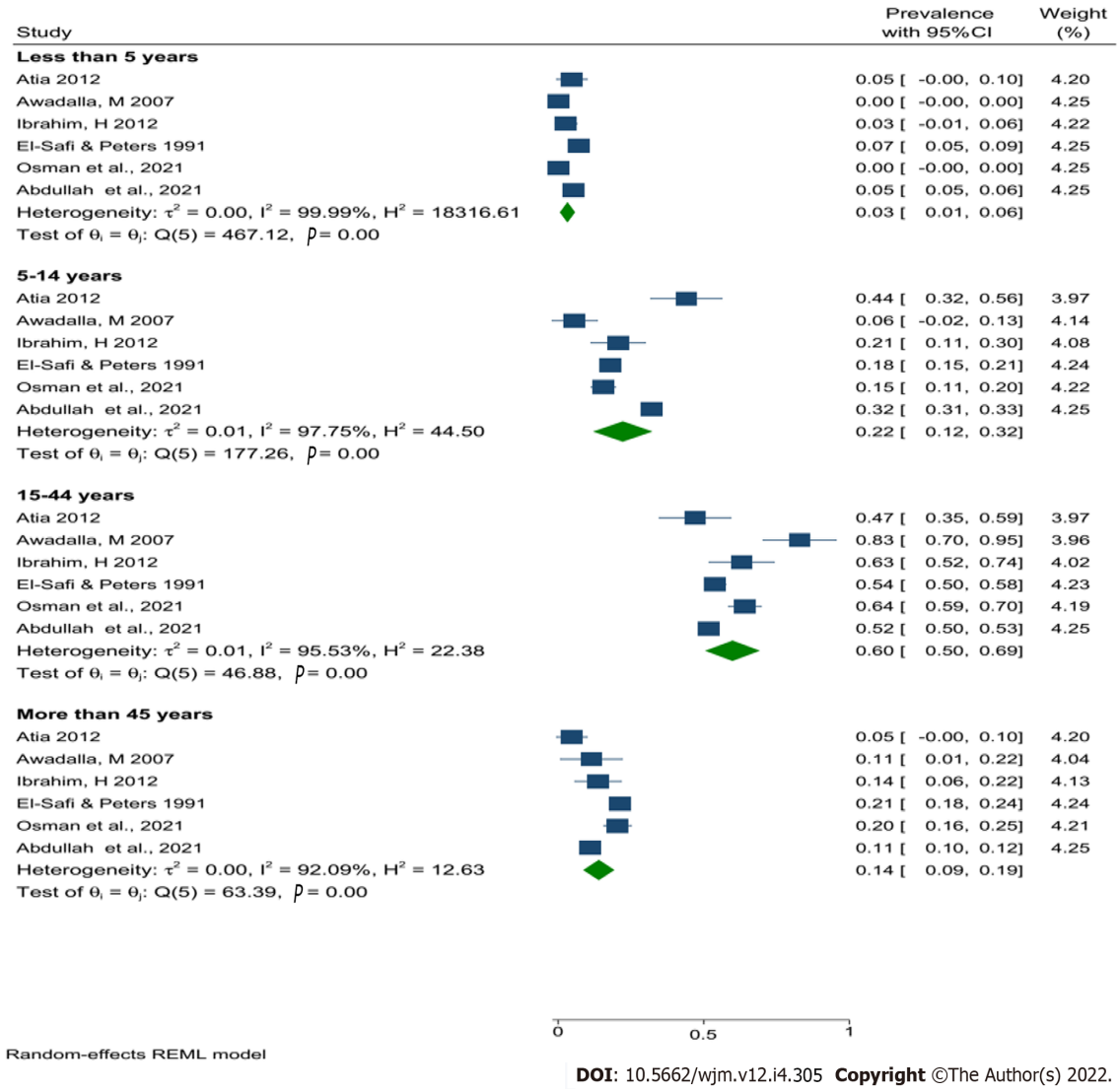

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Figure 5 Forest plot (random-effects model) for the pooled prevalence of human leishmaniasis in different age groups in Sudan.

ARTICLE HIGHLIGHTS

Research background

The prevalence of human leishmaniasis varies widely in different countries and in different regions of the same country. To date, there is no overall estimation of the prevalence of human leishmaniasis in Sudan

Research motivation

The lack of evidence about human leishmaniasis in Sudan may prevent health care policymakers and stakeholders from developing and adopting a suitable prevention program.

Research objectives

The objective of this study was to find the pooled prevalence of leishmaniasis and its associated factors among Sudanese citizens.

Research methods

A systematic literature search was conducted before the 4th of August 2021, from Scopus, Web of Science, PubMed, and MEDLINE, African Journals Online (AJOL), ResearchGate, direct Google search, Google Scholar, and universities websites.

Research results

A total of 20 articles were included in this meta-analysis after 220 articles had been subjected to full-text evaluations, and the overall pooled prevalence of human leishmaniasis in Sudan was 21% (with

confidence interval 12%-30%).

Research conclusions

Human leishmaniasis infection is still endemic in many regions in Sudan and is highly prevalent in central and eastern Sudan, and cutaneous leishmaniasis is the most prevalent in the country.

Research perspectives

More studies need to be done in Sudan to cover all epidemiological aspects of the disease in humans and animals under the umbrella of one health approach, with special emphasis on the health and economic impacts of the disease.

FOOTNOTES

Author contributions: Ahmed M, Abdulslam Abdullah A, Bello I, Hamad S, and Bashir A conceived and designed the review, developed the search strings, and rigorously reviewed the manuscript; Ahmed M, Abdulslam Abdullah A, and Hamad S carried out the draft of the manuscript; Abdulslam Abdullah A is the guarantor of the review; Ahmed M and Abdulslam Abdullah A screened and selected studies, extracted the data, evaluated the quality of the studies, and carried out analysis and interpretation.

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META-ANALYSIS

Pain reduction and adverse effects of intravenous metoclopramide for acute migraine attack: A systematic review and meta-analysis of randomized-controlled trials

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Abstract

BACKGROUND

Metoclopramide may be used to treat people suffering from acute migraine. However, no comprehensive investigation on this issue has been recorded. This review will provide more solid evidence for the use of metoclopramide in treating acute migraine.

AIM

To compare the efficacy of intravenous metoclopramide with other therapies in migraine attack treatment in an emergency department (ED).

METHODS

We included randomized controlled trials of participants older than 18 years with acute migraine headaches, which included at least one arm that received intravenous (IV) metoclopramide at the ED. A literature search of PubMed, Web of Science, Cochrane Collaboration, and Reference Citation Analysis on December 31, 2021 retrieved other drugs or placebo-controlled studies without language limitation. The risk of bias was assessed using the Cochrane risk of bias tool. The primary endpoint was pain reduction at 60 min or closest to 1 h after treatment, as measured by the pain scale. Secondary endpoints included adverse effects or reactions resulting from metoclopramide or comparisons.

RESULTS

Fourteen trials with a total of 1661 individuals were eligible for review. The risk of bias ranged from low to intermediate. IV metoclopramide administration was not associated with higher pain reduction at 1 h (Standard mean difference [SMD] = -0.03, 95% confidence interval [CI]: -0.33-0.28, P = 0.87). However, metoclopramide

was associated with better pain reduction than placebo (SMD = 1.04, 95%CI: 0.50-1.58, P = 0.0002). In addition, side effects were not significantly different between IV metoclopramide and other drugs or placebo (odds ratio [OR] = 0.76, 95%CI: 0.48-1.19, P = 0.09 and OR = 0.92, 95%CI: 0.31-2.74, P = 0.54, respectively).

CONCLUSION

Metoclopramide is more effective than placebo in treating migraine in the ED. Despite the observed tendency of decreased side effects, its effectiveness compared to other regimens is poorly understood. More research on this area is needed to treat migraine in acute care settings effectively.

Key Words: Metoclopramide; Migraine; Efficacy; Adverse effect; Randomized controlled trials

Core Tip: Metoclopramide may be used to treat people suffering from acute migraine. However, no comprehensive investigation on this issue has been recorded. We conducted an up-to-date systematic review and meta-analysis of the clinical efficacy of metoclopramide during an acute migraine attack. This study comprised 14 studies and found that metoclopramide was more effective than placebo in treating migraine at the emergency department. When compared to other medications, however, no substantial advantage was detected. More study is needed to enhance migraine therapy in acute care settings effectively.

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INTRODUCTION

Migraine, a chronic neurological disease, is one of the most common causes that lead patients to seek medical attention[1]. Apart from regular follow-up at the outpatient department, many patients with migraine suffer from acute migraine attacks requiring an emergency department (ED) visit. There were approximately 1.2 million annual ED visits for acute migraine headaches in the United States[2]. At the same time, persons who suffer from this illness frequently encounter several other accompanying symptoms, such as nausea, vomiting, and sensitivity to light, sound, touch, or scent[3,4]. Unfortunately, its pathogenesis remains complicated and little understood. As a result, if such a problem cannot be effectively treated, it significantly impacts the health-related quality of life of individuals suffering from acute migraine[5,6].

According to the American Headache Society recommendations, several acute migraine treatments include triptans, ergotamine, non-steroidal anti-inflammatory drugs, combination analgesic, and anti-emetics[7]. Metoclopramide, an anti-emetic drug acting as a dopamine/serotonin antagonist, was initially used in migraine patients who experienced nauseating symptoms[8]. Later, it was shown to be effective in pain control of acute migraine attacks[9,10]. In the recent recommendation, metoclopramide was considered the "probably effective drug," even though several studies showed the efficacy of metoclopramide monotherapy. It has been investigated that the efficacy of metoclopramide was neither inferior to sumatriptan nor opioids[11,12].

Moreover, apart from the efficacy aspect, metoclopramide showed superiority in other aspects, such as lower adverse severe effects and lower addiction rates which are considered an essential issue in the ED as patients with migraine tend to revisit. It is undeniable that metoclopramide might not be the first choice for clinicians to use in acute migraine as its efficacy might not be outstanding compared to other drugs. As prior mentioned, the severe side effects of metoclopramide, which are extrapyramidal symptoms, such as tardive dyskinesia and akathisia, though rarely reported in short term use and less worrisome than those of triptans and opioids, should also be concerned as they might result in an irreversible and sufferable experience for the patient[11].

To comprehend the big picture of using metoclopramide in acute care for migraine, this study aimed to compare metoclopramide use with other therapy in migraine attack treatment in an acute care setting. Our study hypothesized that metoclopramide monotherapy should effectively treat acute migraine attacks in an ED.

MATERIALS AND METHODS

Protocol

We conducted this systematic review and meta-analysis following the Preferred Reporting Items for Systematic Reviews and Meta-analyses statement guidelines[13]. We prospectively registered our protocol with the International prospective register of systematic reviews (ID: CRD42022322609).

Search strategy and inclusion criteria

We (N.U. and W.W.) independently searched four standard databases, PubMed, Web of Science, Cochrane Collaboration, and Reference Citation Analysis, from their inception until December 31, 2021, without language restriction. The search words "metoclopramide," "Meclopran," "Plasil," "Reglan," "methoxyprocainamide," "migraine," and "headache" were the Medical Subject Headings used, in combination and with different spellings and endings. We also searched websites, organizations, relevant reviews, grey literature, and references to identify additional eligible studies. Additionally, we searched for any unpublished trials registered on the "clinicaltrials.gov" Internet site.

The selection criteria were as follows: (1) Randomized controlled trials including adults more than 18 years of age with acute migraine headaches, regardless of their types (*i.e.*, with or without aura); (2) at least one arm having received an intravenous (IV) metoclopramide during ED stay; (3) comparing of at least one agent or placebo; (4) reporting of average pain scale before the administration of each agent; and (5) reporting of at least one of the following: Pain scale at 60 or other minutes, any adverse effects, and rescue medications needed at the ED. We excluded pre-clinical studies, review articles, and studies without a control group (*e.g.*, case reports and case series). The two authors (N.U. and W.W.) independently screened the search results to identify eligible studies. Full-text articles of the retrieved studies were retrieved and independently assessed by the two authors against the pre-specified criteria (Figure 1). Any discrepancies were discussed with a third party and concluded by consensus.

Outcomes of interests

The primary endpoint was pain reduction at 60 min or closest to 1 h after treatment administration, as measured by the Visual Analog Scale (VAS) or others. Secondary endpoints included adverse effects or reactions resulting from metoclopramide or interventions. Adverse effects in this study were defined by any of the following symptoms: Upper gastrointestinal complaints (dyspepsia, heartburn, and bloating), allergic reaction, dizziness, drowsiness, nasal congestion, dry mouth, dystonic reaction, akathisia, and significant blood pressure drop.

Data extraction and assessment of risk of bias

We separately extracted the data from the included articles using a prepared data extraction form. Specifically, we extracted basic characteristics (first author, publication year, study location and setting, and number and age of participants), treatment details and interventions in the study groups, and the outcomes of interest. We sought to contact the associated author by email for incomplete or missing data or clarification. The two authors (N.U. and W.W.) independently assessed the risk of study bias using the latest version of the Cochrane Collaboration tool for assessing the trial risk of bias[14]. Any disagreements were handled through discussion with the assistance of a third independent expert.

Data synthesis and statistical analysis

The data was imported into pre-formatted record forms. We calculated individuals and pooled estimates as standard mean differences (SMDs) for continuous endpoints, with 95% confidence intervals (CIs). We calculated individuals and pooled estimates using odds ratios (ORs) with CIs for dichotomous endpoints. We estimated heterogeneity among the included studies using the I^2 statistic (the percentage of total variation across studies due to heterogeneity). We applied a fixed-effect model if the heterogeneity was minor ($I^2 \leq 50\%$). However, if there was evidence of strong heterogeneity ($I^2 > 50\%$), a random-effect model was employed instead. Visual assessment of funnel plots and Egger's test were used to assess publication bias caused by small-study effects. For statistical analyses, we applied RevMan version 5.3 (Nordic Cochrane Center, Cochrane Collaboration, 2014, Copenhagen, Denmark) [15]. All tests were two-tailed, and P values < 0.05 were considered statistically significant.

RESULTS

Study selection

Figure 1 demonstrates how the 820 retrieved articles were screened for inclusion in the review and analysis. After excluding duplicated studies, 533 remained. Of those, 470 were excluded following title and abstract screening according to the inclusion and exclusion criteria. The remaining 63 articles were retrieved and reviewed for full-text copies before including 12 studies in the data analysis. In addition, three articles were also searched by citation searching, and two articles met the pre-specified criteria.

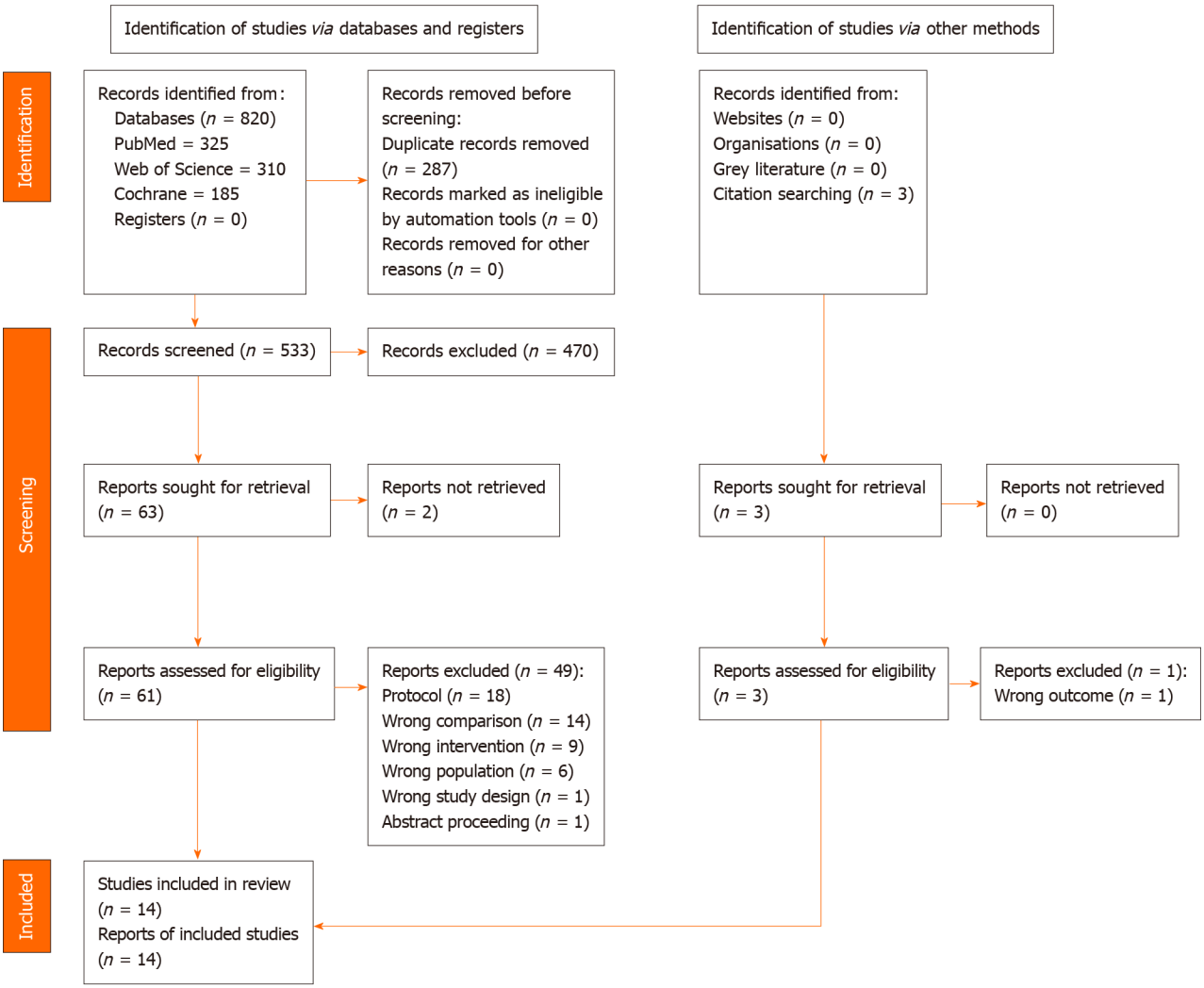

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Figure 1 PRISMA flow chart of study selection.

Finally, 14 articles[10,16-28] with 1661 participants were included in the meta-analysis.

Characteristics of included studies

Data extraction and meta-analysis were performed on 14 papers published between 1990 and 2020. The research was carried out in the United States of America (*n* = 7), Turkey (*n* = 3), and Iran (*n* = 4). The mean ages were around 34-40 years. Most studies applied 10 mg of IV metoclopramide, while three administered 20 mg of metoclopramide as interventions. Five trials investigated the efficacy of IV metoclopramide against placebo. Most studies compared more than one arm. All trials reported pain intensity at 0 and other minutes after drug administration, as VAS or other appropriate methods. Table 1 summarizes the baseline demographics and clinical characteristics of the included studies. Deviation from the intended interventions and randomization contributed to a high proportion of concerns over risk of bias. Five out of fourteen had an overall low risk of bias. The risk of bias assessment by Cochrane risk of bias assessment is illustrated in Figures 2 and 3.

Primary outcome

All 14 studies reported average pain reduction at 60 min or at the time closest to 1 h. The overall effect size showed no statistical significance with regard to the efficacy between IV metoclopramide and other drugs (SMD = -0.03, 95%CI: -0.33-0.28, P = 0.87). However, IV metoclopramide demonstrated a significant pain reduction compared with placebo (SMD = 1.04, 95%CI: 0.50-1.58, P = 0.0002). Subgroup analyses found that IV metoclopramide had a significant advantage in pain reduction compared with subcutaneous sumatriptan (SMD = 0.73, 95%CI: 0.11-1.35, P = 0.03), IV valproate (SMD = 0.27, 95%CI: 0.01-0.54, P = 0.04), and oral ibuprofen (SMD = 1.41, 95%CI: 0.41-2.41, P = 0.006). Heterogeneity was observed among the subgroups comparing IV metoclopramide and other drugs (I^2 = 81.5%, P < 0.0001; Figure 4). Figures 4 and 5 demonstrate the forest plot comparing pain reduction at 60 min between IV metoclopramide and other drugs and placebo, respectively.

Table 1 Baseline demographics and clinical characteristics of included studies

Ref.	Age, year	Intervention	Comparisons	Sample size (intervention/comparisons)	Outcomes of interest
Yavuz *et al* [16], 2020, Turkey	36.8 ± 11.4	IV metoclopramide 10 mg	1 IV dexketoprofen trometamol 50 mg; 2 IV dexketoprofen trometamol 50 mg plus IV metoclopramide 10 mg	150 (50/50/50)	VAS at 0, 15, and 30 min, adverse effects, and requirement of rescue medicine
Khazaei *et al* [17], 2019, Iran	36.8 ± 9.9	IV metoclopramide 10 mg	1 IV dexamethasone 8 mg; 2 IV ketorolac 30 mg; 3 IV chlorpromazine 25 mg	128 (32/32/32/32)	VAS at 0 min, 60 min, and 24 h, adverse effects
Doğan *et al* [18], 2019, Turkey	34 ± 13.3	IV metoclopramide 10 mg	1 Placebo	148 (74/74)	Pain intensity at 30 min, adverse effects, and requirement of rescue analgesic-Change in pain intensity, additional ED visit in 24-72 h after discharge
Amiri *et al* [19], 2017, Iran	33.5	IV metoclopramide 10 mg	1 IV granisetron 2 mg	148 (73/75)	VAS before and at 1, 2, and 4 h after drug administration, emesis episode
Friedman *et al*[20], 2014, USA	33.7 ± 13.1	IV metoclopramide 10 mg	1 IV sodium valproate 1000 mg; 2 IV ketorolac 30 mg	330 (110/110/110)	Verbal NRS and ordinal pain scale every 30 min, adverse effects, and requirement of rescue medication
Talabi *et al* [21], 2013, Iran	30.9 ± 8.0	IV metoclopramide 20 mg	1 SC sumatriptan 6 mg	124 (62/62)	VAS at 0 and 60 min
Friedman *et al*[22], 2004, Turkey	34 ± 4.4	IV metoclopramide 20 mg	1 SC sumatriptan 6 mg	78 (40/38)	NRS at 0, 2, and 24 h, and rate of pain free headache response at 2 and 24 h, rate of modified headache response, associated symptoms, satisfaction, disability score, and requirement for rescue drug
Cete *et al* [10], 2004, Iran	40 ± 12	IV metoclopramide 10 mg	1 IV magnesium sulphate 2 g; 2 Placebo	113 (37/36/40)	VAS at 0, 15, and 30 min, additional analgesic, rescue medication, adverse events in ED, and recurrence rate at 24 h
Ellis *et al* [23], 1993, USA	N/A	IV metoclopramide 10 mg	1 Oral ibuprofen 600 mg; 2 IV metoclopramide 10 mg + PO ibuprofen 600 mg; 3 Placebo	40 (10/10/10/10)	VAS and nausea scores at 0, 30, and 60 min, requirement of rescue medication
Cameron *et al*[24], 1995, USA	32.1 ± 27.0	IV metoclopramide 10 mg	1 IV chlorpromazine 0.1 mg/kg	91 (44/47)	VAS at 0 and every 15 min, requirement of rescue drug
Friedman *et al*[25], 2008, USA	36.0 ± 11.1	IV diphenhydramine 25 mg + IV metoclo-pramide 20 mg	1 IV diphenhydramine 25 mg + IV prochlorperazine 10 mg	77 (38/39)	NRS and pain intensity categorical scale at 0 and every 30 min
Coppola *et al*[26], 1995, USA	N/A	IV metoclopramide 10 mg	1 IV chlorpromazine 10 mg; 2 Placebo	70 (24/22/24)	VAS, nausea, and sedation at 0 and 30 min. Early relapse rate in 48 h
Gaffigan *et al*[27], 2015, USA	29 ± 7.9	IV diphenhydramine 25 mg + IV metoclo-pramide 10 mg	1 IV diphenhydramine 25 mg + IV haloperidol 5 mg	64 (33/31)	Pain, nausea, restlessness, and sedation at 0, 20, 40, 60, and 80 min, requirement of rescue medication, patient satisfaction, adverse events, early discharge, ED revisit, and QT interval
Tek *et al* [28], 1990, USA	N/A	IV metoclopramide 10 mg	1 Placebo	50 (24/26)	Degree of pain relief at 1 h after treatment

ED: Emergency department; IV: Intravenous; N/A: Not applicable; NRS: Numerical rating scale; SC: Subcutaneous; VAS: Visual analog scale.

Secondary outcome

Eight studies measured adverse effects across IV metoclopramide and comparisons. The pooled effect size was homogenous both compared with others (I^2 = 13.3%, P = 0.33; Figure 6) and with placebo (I^2 = 0%, P = 0.89; Figure 7). Adverse effects were not different across IV metoclopramide and other comparisons (OR = 0.76, 95%CI: 0.48-1.19, P = 0.09) or placebo (OR = 0.92, 95%CI: 0.31-2.74, P = 0.54). Subgroup analyses yielded similar results for all comparisons (Figure 6).

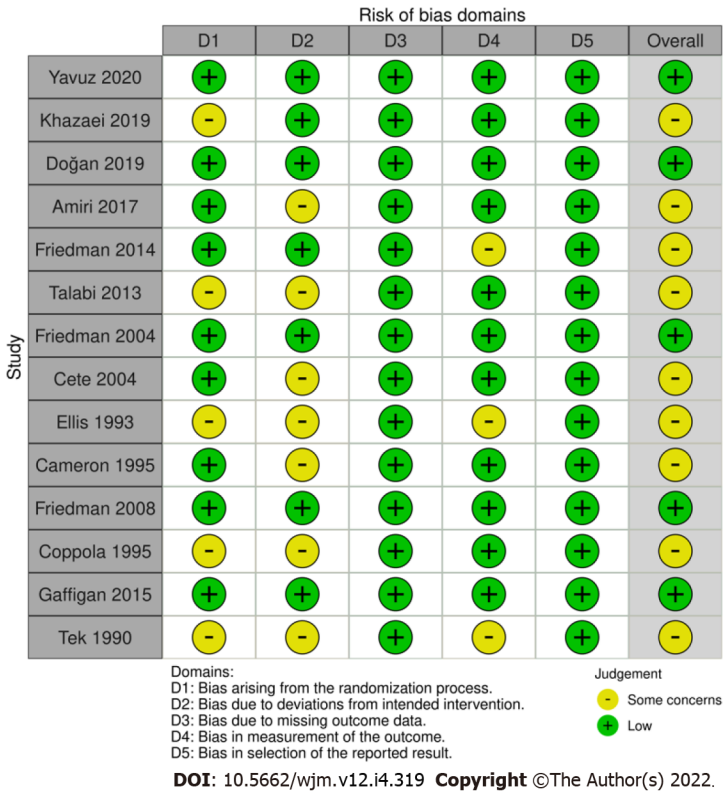

Figure 2 Cochrane risk of bias assessment of included studies.

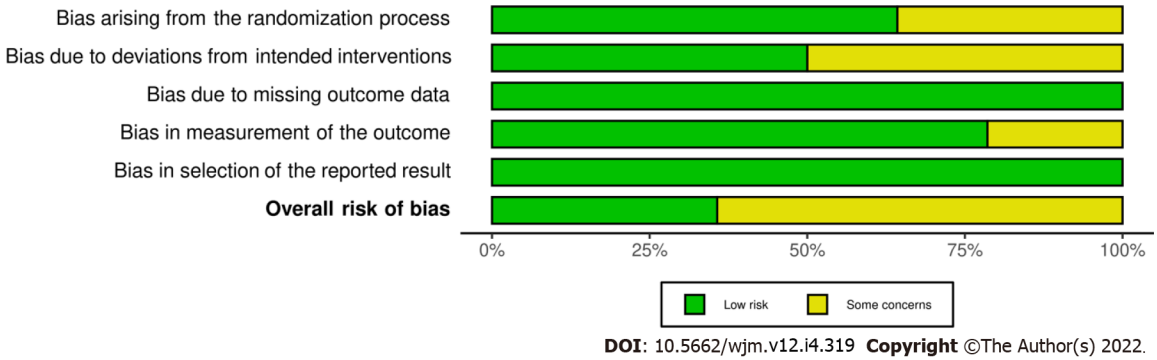

Figure 3 Details of each domain of Cochrane risk of bias assessment.

Publication bias

There was no substantial publication bias in the funnel plot for the meta-analysis of the average pain reduction between IV metoclopramide and comparisons (Figure 8). The regression-based Egger's test was performed using a random-effect model with restricted maximum-likelihood method and found that *P* value was 0.0814.

DISCUSSION

This meta-analysis investigated the clinical efficacy of IV metoclopramide for treating acute migraine attacks in the ED. This study showed that administration of IV metoclopramide was an effective treatment for migraine headache in adults, compared with placebo. However, the benefit of metoclopramide was not superior to other drugs. Our systematic review also demonstrated that IV metoclopramide tended to have fewer side effects than other interventions. The overall study risk of bias ranged from low to some concerns.

Acute migraine is a common neurovascular disorder. It is described as a moderate to severe, predominantly unilateral, and recurrent headache that lasts for several hours to a few days[3,29]. Metoclo-

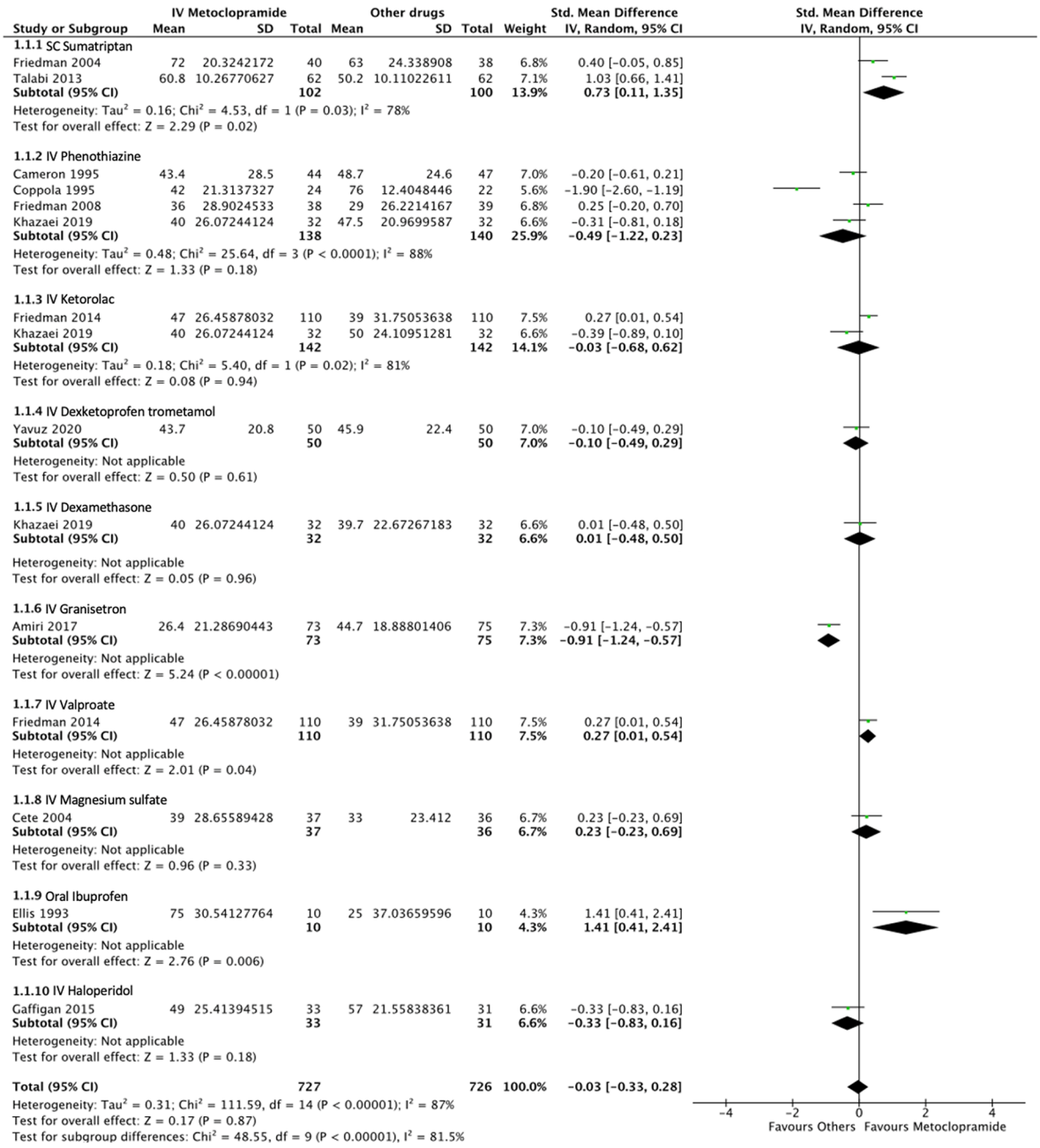

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Figure 4 Forest plot comparing pain reduction at 60 min between intravenous metoclopramide and other drugs. CI: Confidence interval; IV: Intravenous; SC: Subcutaneous.

pramide is initially used to treat acute migraine for decades[11]. A few studies over the years have highlighted that metoclopramide has substantial therapeutic effectiveness in treating acute migraine episodes[26,30]. The reason behind the use of metoclopramide could be that it antagonizes the dopamine D2 receptor, which is proposed to be one of the pathogeneses of pain in migraine[11]. A meta-analysis of pooled data illustrated that metoclopramide significantly reduced headache pain, and those patients were less likely to rescue medicines than the placebo groups[3]. However, the authors chose various inclusion and exclusion criteria for this study, which may contain data on non-migraine headaches, confounding any conclusions to be derived[3]. Furthermore, metoclopramide also had an anti-emetic effect that ameliorates migraine patients' symptoms[11]. Therefore, metoclopramide could be a first-line treatment for acute migraine episodes. Our findings are consistent with the prior research finding that metoclopramide was more effective than placebo in pain reduction[9]. In addition, metoclopramide had a higher benefit than some drugs in our analysis (subcutaneous sumatriptan, intravenous valproate, and oral ibuprofen). These findings fit with the pattern described previously by Colman *et al* [9]. However, that study selected both ED and headache clinic settings, which differed from ours. Besides, Colman and colleagues analyzed the pain using a complete relief of headache or significant reduction in headache pain. As a result, discrepancies were likely to occur across that definition. Our

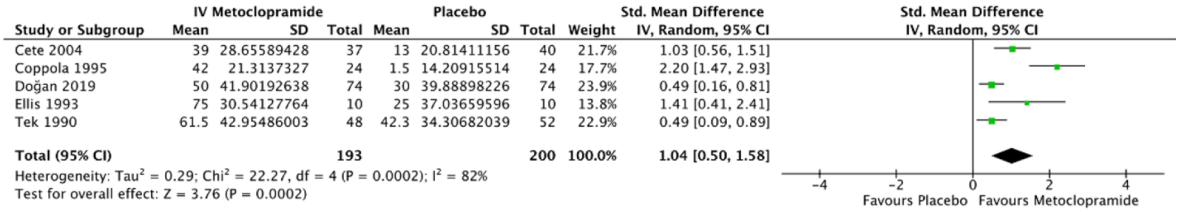

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Figure 5 Forest plot comparing pain reduction at 60 min between intravenous metoclopramide and placebo. CI: Confidence interval; IV: Intravenous.

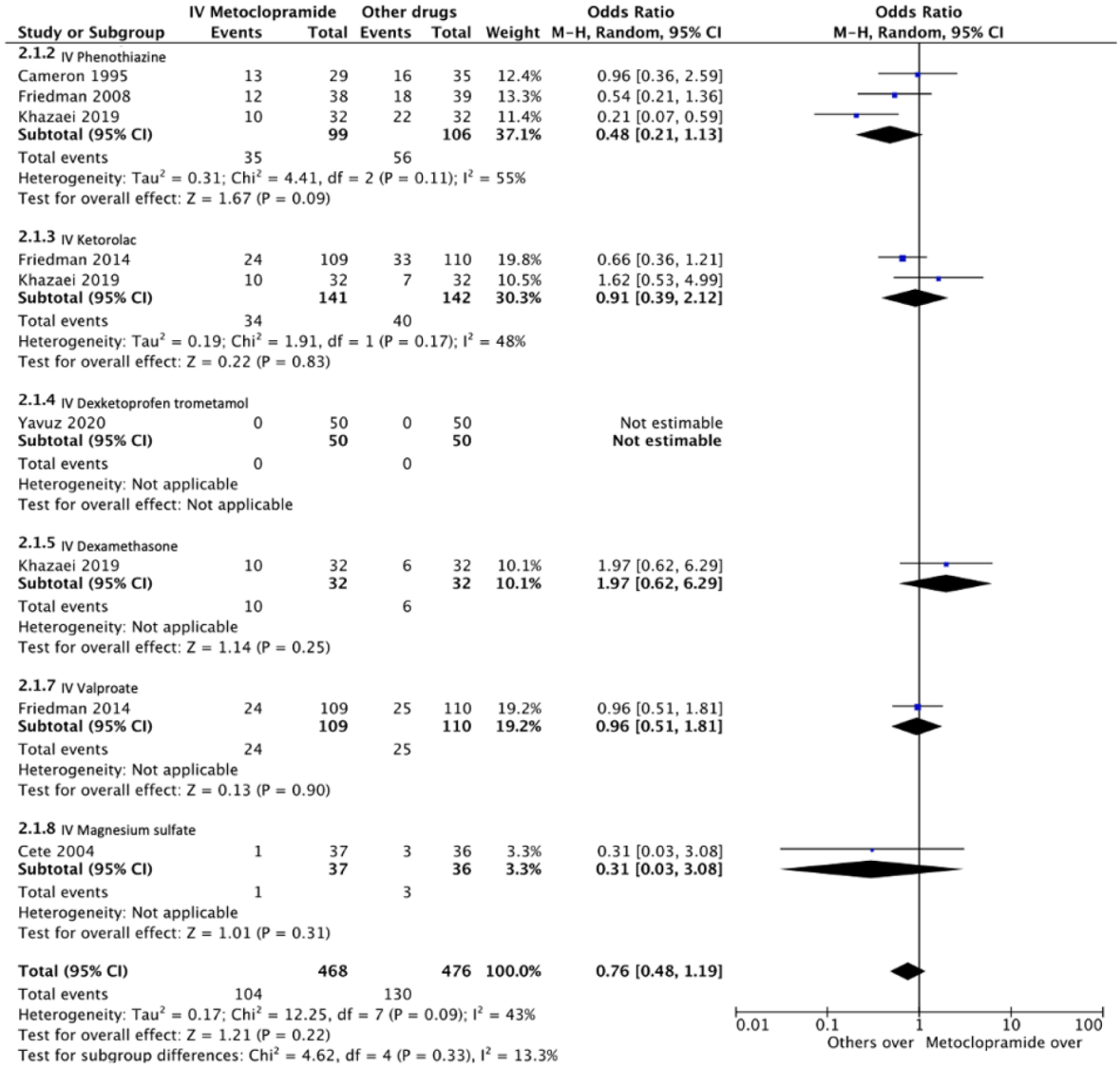

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Figure 6 Forest plot comparing odds ratios of adverse effects between intravenous metoclopramide and other drugs. CI: Confidence interval; IV: Intravenous.

study provided the difference aiming to close this gap. We compared all studies based on the pre- and post-intervention mean pain intensity in each study, which is more feasible to apply and compare.

However, the side effects of metoclopramide might be serious and irreversible, for example, tardive dyskinesia. It is characterized by the uncontrollable movement of the tongue, face, and extremities. Nonetheless, our findings reveal that the adverse effects resulting from metoclopramide were not different across the other drugs. Results obtained by Orr and colleagues[31] are consistent with our findings. Moreover, compared to other suggested therapies, metoclopramide's adverse effect profile is less concerning than triptans, which are commonly utilized in ED situations[32,33].

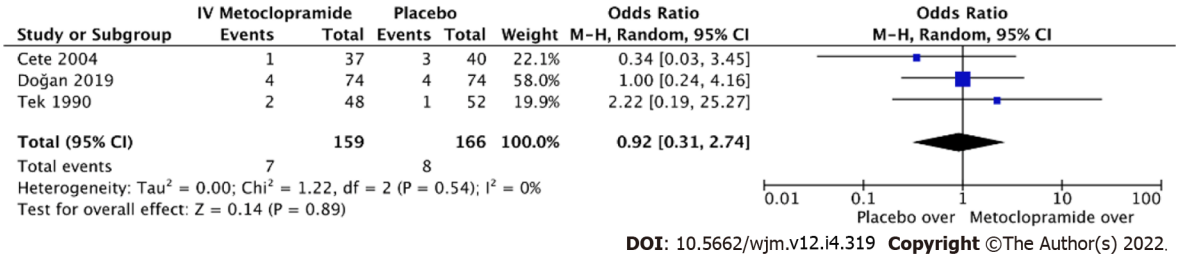

Figure 7 Forest plot comparing odds ratios of adverse effects between intravenous metoclopramide and placebo. CI: Confidence interval; IV: Intravenous.

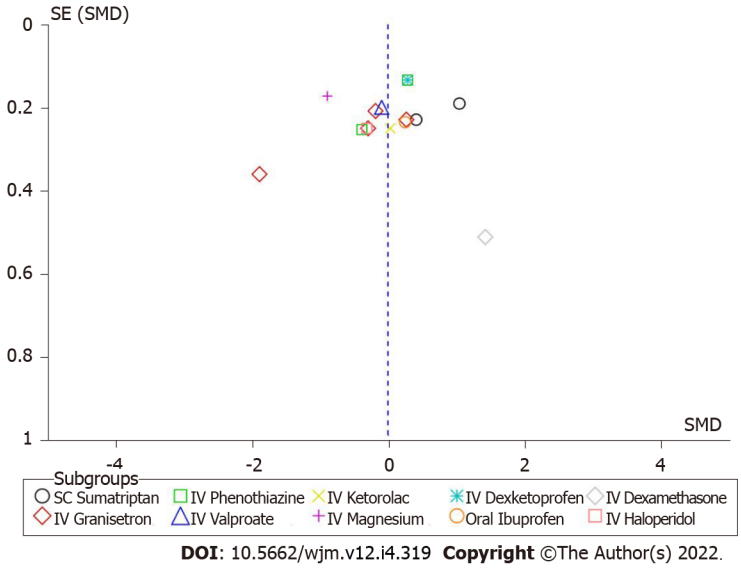

Figure 8 Funnel plot of pain reduction at 60 min between intravenous metoclopramide and other drugs. IV: Intravenous; SC: Subcutaneous; SE: Standard error; SMD: Standard mean difference.

Limitation

This review contains some limitations. First, all included studies were conducted in only three countries, including Iran, United States, and Turkey, which possibly resulted in the generalizability bias. Secondly, most trials did not report exclusion criteria in sufficient detail; therefore, the definitions for migraine might be varied among studies. In addition, several studies did not report the confirmation of migraine diagnosis, duration of headache, and prior therapies. As a result, we probably combined studies with varying patient characteristics, making it difficult to determine if our findings are generalizable to other contexts. Finally, this meta-analysis included studies done at different dates (between 1990 and 2020), resulting in the observed heterogeneity.

CONCLUSION

To conclude, metoclopramide was proven to be beneficial to treating migraine in the acute care setting, such as in the ED, compared to placebo. Despite the demonstrated trend of a lower adverse effect, its efficacy compared to other regimens is little comprehended. More studies on this topic should be further conducted to improve migraine treatment in acute care settings effectively.

ARTICLE HIGHLIGHTS

Research background

Metoclopramide may be used to treat people suffering from acute migraine. However, no comprehensive investigation on this issue has been recorded. This review will provide more solid evidence for the use of metoclopramide in treating acute migraine.

Research motivation

Metoclopramide was considered the "probably effective drug", even though several studies showed the efficacy of metoclopramide monotherapy. It has been investigated that the efficacy of metoclopramide was neither inferior to sumatriptan nor opioid. Moreover, apart from the efficacy aspect, metoclopramide showed superiority in other aspects, such as lower adverse severe effects and lower addiction rates.

Research objectives

The objective of this review was to investigate the efficacy of intravenous metoclopramide with other therapies in migraine attack treatment in an emergency department (ED).

Research methods

We conducted a systematic review and meta-analysis of randomized controlled trials.

Research results

The administration of received intravenous metoclopramide was an effective treatment for migraine headache in adults, compared with placebo. However, the benefit of metoclopramide was not superior to other drugs.

Research conclusions

Metoclopramide is more effective than placebo in treating migraine in the ED. Although its effectiveness was not observed on other medications, clinicians may select metoclopramide as one of the first line treatments for acute migraine.

Research perspectives

Despite the observed tendency of decreased side effects, the effectiveness of metoclopramide compared to other regimens is poorly understood. More research on this area is needed to treat migraine in acute care settings effectively.

FOOTNOTES

Author contributions: Ungrungseesopon N and Wongtanasarasin W designed the protocol, contributed to data collection and analysis, and wrote the first draft of the manuscript; Wongtanasarasin W edited and revised the manuscript; both authors read and critically reviewed the final version of the manuscript.

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