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Contents

Bimonthly Volume 12 Number 5 September 20, 2022

REVIEW

MINIREVIEWS

ORIGINAL ARTICLE

Observational Study

SYSTEMATIC REVIEWS

META-ANALYSIS

World Journal of Methodology

Bimonthly Volume 12 Number 5 September 20, 2022

Contents

LETTER TO THE EDITOR

World Journal of Methodology

Bimonthly Volume 12 Number 5 September 20, 2022

Contents

ABOUT COVER

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REVIEW

Hemostatic system and COVID-19 crosstalk: A review of the available evidence

Mohamed-Naguib Wifi, Mohamed Abdelkader Morad, Reem El Sheemy, Nermeen Abdeen, Shimaa Afify, Mohammad Abdalgaber, Abeer Abdellatef, Mariam Zaghloul, Mohamed Alboraie, Mohamed El-Kassas

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Abstract

Since the discovery of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and its resultant coronavirus disease 2019 (COVID-19) pandemic, respiratory manifestations have been the mainstay of clinical diagnosis, laboratory evaluations, and radiological investigations. As time passed, other pathological aspects of SARS-CoV-2 have been revealed. Various hemostatic abnormalities have been reported since the rise of the pandemic, which was sometimes superficial, transient, or fatal. Mild thrombocytopenia, thrombocytosis, venous, arterial thromboembolism, and disseminated intravascular coagulation are among the

many hemostatic events associated with COVID-19. Venous thromboembolism necessitating therapeutic doses of anticoagulants is more frequently seen in severe cases of COVID-19, especially in patients admitted to intensive care units. Hemorrhagic complications rarely arise in COVID-19 patients either due to a hemostatic imbalance resulting from severe disease or as a complication of over anticoagulation. Although the pathogenesis of coagulation disturbance in SARS-CoV-2 infection is not yet understood, professional societies recommend prophylactic antithrombotic therapy in severe cases, especially in the presence of abnormal coagulation indices. The review article discusses the various available evidence on coagulation disorders, management strategies, outcomes, and prognosis associated with COVID-19 coagulopathy, which raises awareness about the importance of anticoagulation therapy for COVID-19 patients to guard against possible thromboembolic events.

Key Words: SARS-CoV-2; COVID-19; Thrombosis; Pulmonary embolism; Disseminated intravascular coagulation

Core Tip: The pathogenesis of hypercoagulable state and thrombosis related to coronavirus disease 2019 (COVID-19) is unclear. Evidence on endothelial cell injury by direct infection of severe acute respiratory syndrome coronavirus 2 is increasing. Histologic and immunohistochemistry examination of lung autopsies and/or the skin of patients who have died of severe COVID-19 has shown microvascular injury and thrombosis, consistent with intensive and generalized activation of both alternative and lectin-based pathways of complement.

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INTRODUCTION

One of the frequently encountered complications of systemic infections is activation of the coagulation cascade, which can present with a broad spectrum of clinical manifestations varying from subclinical activation, which is expressed by elevated laboratory markers for thrombin and fibrin products, to disseminated intravascular coagulation (DIC) and resultant formation of microvascular thrombi in various body tissues and organs[1]. Inflammation affects all phases of blood coagulation, which in turn, leads to both thrombotic as well as hemorrhagic complications[2]. Various viral infections, such as the human immunodeficiency virus, Dengue virus, and Ebola virus, occur by activation of the coagulation cascade[3-5]. Either direct or indirect activation of endothelial cells by viral infection can affect the balance between the coagulation and fibrinolytic systems[6,7]. The clinical presentation of this altered coagulation appears in hemorrhage, thrombosis, or both. An exaggerated response may even lead to DIC with the formation of microvascular thrombi in various organs[8]. Tissue factor (TF) expression is increased in herpes simplex virus and Dengue virus-infected endothelial cells[9].

The Ebola virus induces TF expression in circulating blood cells, especially macrophages, a condition known as Ebola hemorrhagic fever[4,9]. Stimulation by the poly I:C toll-like receptor 3 (TLR3) agonist induces activation of many proinflammatory cytokines as an antiviral chemokine, which is a selective chemoattractant for both activated type 1 T lymphocytes and natural killer cells. Thus, poly I:C increases TF expression in cultured endothelial cells and activates the coagulation system in mice [4]. On the other hand, inhibition of the TF/factor VIIa (FVIIa) complex was shown to decrease the cytokine storm and mortality in a rhesus monkey model of Ebola hemorrhagic fever[10]. Other hematological disorders that frequently occur with viral infections are hemolytic uremic syndrome, idiopathic thrombocytopenic purpura, and thrombotic thrombocytopenic purpura[7]. However, it is not clear why some viruses cause hemorrhage while others are associated with thrombosis as cytomegalovirus or both complications such as varicella-zoster virus[10,11].

Viral respiratory tract infections carry a higher risk for deep venous thrombosis and possibly pulmonary embolism (PE)[12]. Influenza A virus is associated with DIC and 18 pulmonary microembolism[13,14]. In the influenza A virus subtype H1N1, both thrombotic and hemorrhagic complications have been reported such as deep vein thrombosis (DVT), PE, and pulmonary hemorrhage with

hemoptysis, hematemesis, petechial rash, and one case of disseminated petechial brain hemorrhage[15]. Another example of viral infection associated with coagulopathy is H5N1, the highly pathogenic avian influenza that results in DIC, pulmonary hemorrhage, and thrombocytopenia in many cases[16]. The outbreak of severe acute respiratory syndrome (SARS) has been associated with significant morbidity and mortality caused by a broad spectrum of clinical presentation, *e.g.*, DIC, deep venous thrombosis, and pulmonary thromboembolic disasters resulting in pulmonary infarction, due to activated coagulation and vascular endothelial damage in both small and mid-sized pulmonary vessels[17].

Due to the ambiguity of the pathogenesis of the hypercoagulable state related to coronavirus disease 2019 (COVID-19) and the evidence of endothelial cell injury by direct infection with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus, histologic and immunohistochemistry examination of lung autopsies and/or skin of patients who died of severe COVID-19 showed microvascular injury and thrombosis. This review discusses the evidence of coagulation disorders, management strategies, outcome, and prognosis associated with COVID-19 coagulopathy to guard against possible thromboembolic events.

DATA FROM SARS-COV-1 AND MIDDLE EAST RESPIRATORY SYNDROME

SARS-CoV or SARS-CoV-1 emerged in China in 2003 and spread to another 26 countries and is associated with thrombotic complications and hematologic disorders. Histopathological examination of pulmonary vasculature has revealed fibrin thrombi in pulmonary, bronchial, and small lung veins. Many studies of postmortem autopsies identified PE, DVT, and widespread multi-organ infarcts due to thrombi associated with polyangiitis and microcirculation disturbance as ischemic stroke (IS). SARS-CoV-1 causes placental circulation dysfunction through fibrin deposition, avascular and fibrotic villi formation, and prothrombotic tendency resulting in many intrauterine fetal complications such as oligohydramnios, intrauterine growth delay, and small fetal size[18,19]. Laboratory parameters of SARS-CoV-1-infected patients show prolonged prothrombin time (PT), prolonged activated partial thromboplastin time (especially over the first 2 wk), elevated D-dimer, and worsening thrombocytopenia. Increased thrombopoietin level has been reported in SARS-CoV-1 patients in the convalescent phase compared to normal controls with a concomitant increase in platelet count. Anticardiolipin antibodies have been detected in patients with post-SARS osteonecrosis and those with positive lupus anticoagulant tests in children[20,21]. *In vitro* studies have revealed that some genes have procoagulant effects when expressed in SARS-CoV-1-infected mononuclear cells. TLR9 and thromboxane A synthase genes are the targets of the SARS-CoV-1, where the TLR9 receptor is expressed in platelets to increase platelet activation, degranulation, and aggregation while increased thromboxane production promotes vasoconstriction, platelet aggregation, and endothelial dysfunction[22-24]. Upregulation of the five genes is associated with changes in the coagulation pathway in human hepatoma cells. These genes are: (1) The TF pathway inhibitor 2, which usually inactivates the tissue factor-VIIa complex and thrombin generation, and upon upregulation, it counteracts the mechanism that inhibits overt coagulation cascade activation in response to inflammation; (2) Early growth response 1; (3) Plasminogen activator inhibitor 1, which causes inhibition of fibrinolysis and promotes fibrin deposition during inflammatory states; (4) Phospholipid scramblase 1; and (5) Thrombospondin 1[25-27]. Urokinase pathway dysregulation is involved in the pathogenesis of SARS-CoV-1-related coagulation disorders leading to fatal disease in mice. The nucleocapsid protein of SARS-CoV-1 is one of the determinants of the prothrombotic state caused by SARS-CoV-1 as it induces the human fibrinogen-like protein-2 prothrombinase gene with activation of the C/EBP-α transcription factor[28-31]. The Middle East respiratory syndrome (MERS-CoV) that occurred in Saudi Arabia in 2012 is also associated with thrombotic complications and hematologic manifestations. Histopathologic examination of MERS-CoV-infected patients revealed microthrombi on day 4 of infection in the pulmonary vessels associated with parenchymal consolidation, alveolar edema, and cellular infiltrates. Thrombocytopenia was identified in the 1st week of laboratory-confirmed MERS-CoV cases with relatively lower platelet count in MERS-CoV patients than negative controls. DIC was one of the major complications reported in fatal MERS-CoV infections[32-34].

PATHOGENESIS OF COVID-19-RELATED THROMBOSIS

The pathogenesis of hypercoagulable state and thrombosis related to COVID-19 is unclear. Evidence on endothelial cell injury by direct infection of the SARS-CoV-2 virus is increasing. Histologic and immunohistochemistry examination of lung autopsies and/or skin of patients who died of severe COVID-19 showed microvascular injury and thrombosis, consistent with intensive and generalized activation of both alternative and lectin-based pathways of complement[35]. Subsequent activation of the clotting pathway, causing fibrin deposition, might also be implicated[36]. The hypercoagulable state due to profound derangement of hemostasis is another contributor to venous thromboembolism (VTE), PE, and/or DVT of the lower limbs, which has been observed in patients with COVID-19. There is

controversy about the pattern of hypercoagulability associated with COVID-19. Viral, bacterial, or fungal infection elicits a complex systemic inflammatory response as a part of innate immunity. Activation of the host defense mechanism induces subsequent coagulation and thrombin formation as a critical interaction between humoral and cellular mechanisms, a term called thromboinflammation or immunothrombosis[37]. Severe inflammation in patients with COVID-19, proved by elevated levels of interleukin 6 (IL-6), increased erythrocyte sedimentation rate, increased C-reactive protein (CRP), and elevated fibrinogen at presentation[38], results in subsequent activation of coagulation and may cause elevation of D-dimer levels[39]. Some experts have postulated that the predominant hypercoagulability in patients with COVID-19 suggests a unique hypercoagulable multifactorial state termed thromboinflammation or COVID-19-associated coagulopathy (CAC), which seems to be inconsistent with DIC, even though DIC has been reported in severely ill patients[40,41]. Other potential pathogenesis for coagulation abnormalities in patients with COVID-19 includes antiphospholipid antibodies, anticardiolipin and anti–β2-glycoprotein I immunoglobulin G (IgG) and IgA[42]. Another explanation for coagulation abnormalities in the presence of lupus anticoagulant has been observed in a high percentage (88%-91%) of COVID-19 patients[43,44].

Although COVID-19 pathogenesis is associated with pulmonary intravascular coagulopathy (PIC) and thrombosis, it differs from sepsis-associated DIC. The first explanation of the pathogenesis of PIC and thrombosis in COVID-19 was directed to binding of SARS-CoV-2 to angiotensin converting enzyme-2 receptors that are located on type II pneumocytes (and possibly on vascular endothelial cells). This binding results in lysis of the cells immediately causing activation of the endothelium and procoagulant activity with the activation of fibrin deposits and accumulation in pulmonary microcapillary venous vessels, finally ending in PIC and thrombosis[45]. The second opinion is that the immune-mediated mechanism results in marked microvascular thrombosis and hemorrhage linked to extensive alveolar and interstitial inflammation, sharing features with macrophage activation syndrome in terms of lung-restricted vascular immunopathology associated with COVID-19[46].

In this context, infection with COVID-19 presumably induces a process of immune system hyperactivation known as immunothrombosis, in which activated neutrophils and monocytes interact with platelets and the coagulation cascade, leading to intravascular clot formation in small and larger vessels. It is presumed that the exaggerated immunothrombosis that occurs within lung microvessels is the main driver of COVID-19 manifestations[47,48].

Endothelial dysfunction is thought to be the most striking pathophysiological event in COVID-19 that infects vascular endothelial cells leading to cellular damage and apoptosis, decreasing the antithrombotic activity of the normal endothelium[49-51].

Similar to other respiratory infections, leukocyte recruitment to the lungs, a higher percentage of macrophages and neutrophils together with higher levels of proinflammatory cytokines (*e.g.*, IL-6, IL-8, and IL-1β) and chemokines (*e.g.*, CCL2, CCL3, CCL4, and CCL7) found in the bronchoalveolar fluid are major contributors to inflammatory responses in COVID-19 infection[52].

Until recently, the association between COVID-19 and VTE, including PE and DVT, has been published as case reports. The prevalence of VTE in COVID-19 patients appears to be higher than that reported for patients admitted to intensive care units (ICUs) for other disease conditions[53]. Diagnosis of VTE was 12.7% in COVID-19 patients, as shown in a meta-analysis of multiple studies including 1783 ICU patients[54]. Patients with COVID-19 had some laboratory abnormalities, including a marked increase in D-dimer and, in some cases, mild thrombocytopenia, similar to DIC. However, other coagulation parameters in COVID-19, including high fibrinogen and high factor VIII activity, suggest that coagulation factors' consumption is not evident are inconsistent with DIC. Studies based on biochemical markers such as a marked increase of fibrin degradation products (FDP) (*e.g.*, D-dimer), prolonged PT/activated partial thromboplastin time (aPTT), and low platelet counts were compatible with the state of DIC. However, prolonged PT/aPTT is not confirmed in some studies[55]. Other studies using thromboelastography (TEG), a method of testing the efficiency of blood coagulation, together with biochemical parameters, demonstrated that results observed in patients with COVID-19 are not compatible with DIC[55]. In this context, careful monitoring of PT, platelet count, and D-dimer concentrations may help predict the clinical improvement and the expected complications.

EPIDEMIOLOGY AND CLINICAL PRESENTATION OF THROMBOTIC EVENTS IN COVID-19

Despite the plethora of publications regarding SARS-CoV-2, there are no available solid epidemiologic data on the actual prevalence and incidence of hemostatic derangements among patients. Most available data to date are retrospective observational data and can be classified as case series from a single-center experience that cannot be considered a true reflection of the prevalence and incidence of hemostatic derangements associated with SARS-CoV-2. However, there is some light at the end of the tunnel as the World Health Organization registry has several ongoing prospective studies aimed towards accurately determining the incidence. For example, a French study located in Centre Hospitalier Universitaire de Nice, started February 28, 2020[56], aims to screen prospectively any cardiovascular complication in

COVID-19 patients including PE, DVT, and VTE. Another study initiated in Shandong Provincial Hospital[57], where patients are recruited with novel coronavirus pneumonia (NCP), aims to calculate the rates of venous thrombosis among those patients and determine the risk factors. The Centre Hospitalier Universitaire de Nîmes registered in April 2020 is conducting a more dedicated study[58] to analyze coagulopathy. They observed any abnormality resulting from sepsis, including coagulopathy and DIC, and excluded all factors that would alter or influence outcomes such as pregnancy and lactation, anticoagulants, or antiplatelet therapy before recruitment or those with hypercoagulable states. In a study on 81 ICU hospitalized patients with NCP in Wuhan, 25% (20/81) had VTE with a significant increase in their D-dimer levels[59]. Dutch published data from three hospitals (184 patients) found that the cumulative incidence of thrombotic complications was 31%, most commonly PE (in 25 patients), VTE in 27%, and arterial thrombosis in 2.7% of all thrombotic events, despite receiving standard thromboprophylaxis[60]. In Italy, 22.2% of 54 ICU-admitted patients developed VTE despite prophylactic low molecular weight heparin (LMWH)[61].

Thrombocytopenia is one of the earliest observations in COVID-19 patients. A meta-analysis of nine studies suggested that thrombocytopenia was significantly associated with the severity of COVID-19, with more platelets found in non-survivors. Alhazzani *et al*[62] presented the data of 1099 patients from 522 hospitals and found that 36.2% of those patients had thrombocytopenia, which was even more evident in more severe cases (57.7%) *vs* 31.6% in non-severe cases[62]. However, in another case study performed on 150 COVID-19 patients in ICU, PE was reported in 43% of cases, besides extracorporeal circuit clotting, which was detected in 28 of 29 patients on renal dialysis. This research compared a group of patients with COVID-19 related acute respiratory distress syndrome (ARDS) *vs* non-COVID-19 ones and demonstrated a higher incidence of thrombotic events among COVID-19 patients[43]. In another series of 107 ICU-admitted COVID-19 cases, PE was found in 22% of cases despite receiving prophylactic anticoagulation[61]. VTE was noted in 39% of COVID-19 ICU cases in a case series composed of 74 patients, yet it was demonstrated in 25% of severe COVID-19 pneumonia patients in an earlier case series done on a cohort of 81 patients[59,63].

In a screening study done on 26 COVID-19 severely infected patients using Doppler lower limb ultrasound, VTE was detected in around 69% of patients; besides, bilateral DVT was demonstrated in 38% of cases though they were all on prophylactic anticoagulation therapy[64].

One of the earliest alarming laboratory findings observed in COVID-19 patients requiring hospitalization was marked elevation of the D-dimer. Elevated D-dimer levels are correlated with disease intensity and with high levels of proinflammatory cytokines, suggesting a possible relation between hypercoagulability and inflammation[65].

Different arterial thrombotic events have also been described in COVID-19 patients, and at the top of the list are ischemic central nervous system events. In a study performed in New York, 5 COVID-19 patients demonstrated large vessel occlusion and IS, astonishingly all these patients were young (under 50 years)[66]. Moreover, IS was noticed in 3.7% of patients in another case series composed of 184 COVID-19 patients[60]. Acute limb ischemia is the second most common arterial thrombotic event observed in COVID-19 patients. A recent study demonstrated acute lower limb arterial thrombosis in 20 COVID-19 patients; most were men with an average age above 75 years[67]. Another study reported acute lower limb ischemia in 4 patients, but they were young and did not suffer comorbidities[68]. Myocardial infarction was also described in COVID-19 patients and was reported in 2 Chinese studies [69,70]. Figure 1 demonstrates the hemostatic system and COVID-19 interplay, possible complications, organs affected and outcomes.

LABORATORY ABNORMALITIES AND DIAGNOSTIC WORKUP

COVID-19 patients may have many hemostatic abnormalities (which may result in a hypercoagulable state as illustrated in Table 1[71-74]), so appropriate evaluation is mandatory for the correct diagnosis and management of COVID-19-associated thrombosis. Thromboinflammation or CAC is the predominant coagulation abnormality in COVID-19 patients, which will lead to a hypercoagulable state; it seems to be distinct from DIC, although DIC has been reported in severely affected patients[75]. A unique coagulopathy and procoagulant endothelial phenotype associated with a proinflammatory state with COVID-19 infection have a prominent effect on elevation of fibrinogen and D-dimer/fibrin(ogen) degradation products, which in turn results in systemic hypercoagulation and frequent venous thromboembolic events[76].

It is well known that the high level of D-dimer in COVID-19 is triggered by excessive clots and hypoxemia, which is likely reflecting pulmonary vascular bed thrombosis and fibrinolysis and correlates significantly with mortality. In many retrospective studies conducted in COVID-19 pneumonia patients, elevated baseline D-dimer levels are observed with inflammation. However, they cannot be accurately correlated with VTE score, which could help determine whether this is possible anticoagulation is needed or not based on levels of D-dimer[76,77].

The most common hemostatic abnormalities with COVID-19 include mild thrombocytopenia[78]; as reported in the literature, the incidence of thrombocytopenia ranges between 5%–41.7% of COVID-19

Table 1 The various hematological parameters in significant relation to coronavirus disease 2019 and their mechanisms

Hematological parameter	Significant relation to COVID-19	Mechanism
High RDW (greater than 14.5%)	Increase in mortality risk (from 11% to 31%)[86]	Not completely understood however reports suggested elevated RDW was attributed to affection of RBC production kinetics[86]
Leucopenia or lymphopenia (ALC < 1.0 × 10^9/L)	Observed in most of COVID cases especially hospitalized patients and associated with poor prognosis[86]	(1) Defective immune response; and (2) Drug induced as with steroids[87]
Normal or increased platelet count	Found in some cases of COVID-19	May be caused by to the large amounts of platelets produced in response to increased thrombopoietin formation from liver stimulation and megakaryocytes in the lung[88]
Prolonged PT and aPTT, elevations of D dimer, fibrinogen and FDP and decreased levels of antithrombin III	Direct relationship was observed between severity of COVID and affection of coagulation profile, Overt DIC (ISTH score of 5 and higher) is seen more frequently in non-survivors[89]	aPTT prolongation is caused by increased Factor VIII level and Factor XII deficiency secondary to the presence of factor XII inhibitors. Von Willebrand factor is quantitatively increased. LA is positive in 91% of those with prolonged aPTT. The presence of both LA and Factor XII deficiency are not associated with bleeding tendency

ALC: Absolute lymphocyte count; aPTT: Activated partial thromboplastin time; COVID-19: Coronavirus disease 2019; DIC: disseminated intravascular coagulation; ISTH: International Society on Thrombosis and Hemostasis; LA: Lupus anticoagulant; PT: Prothrombin time; RBC: Red blood cell; RDW: Red cell distribution width.

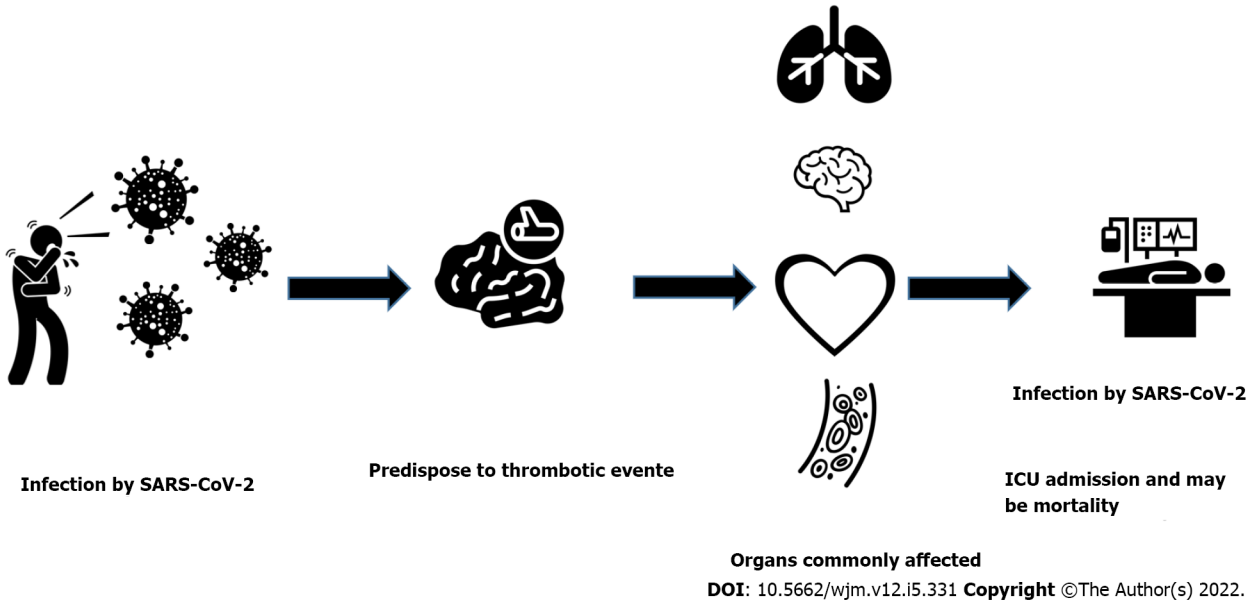

Figure 1 Hemostatic system and coronavirus disease 2019. All icons above are from http://thenounproject.com. ICU: Intensive care unit; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2.

infected patients, and it varies according to the disease severity. Moreover, rebound thrombocytosis was also reported in some cases[79,80]. Several mechanisms of COVID-19-associated thrombocytopenia have been reported, such as direct viral-platelet interaction activation, platelet autoantibody formation, subsequent platelet clearance, splenic/hepatic sequestration, and/or marrow/megakaryocyte suppression owing to inflammatory response, direct viral infection, or reduced thrombopoietin level [81].

One study suggested that patients with COVID-19 have higher platelet counts than patients with other coronavirus infections[82] and elevation of D-dimer[83], which were related to increased risk of requiring mechanical ventilation, and death[65]. However, high D-dimer levels are common in acutely ill individuals with various infectious and inflammatory diseases. Disease severity is variably related to PT prolongation[84], thrombin time[85] and shortened aPTT[86]. The retrospective analysis of 99 COVID-19 patients conducted by Wuhan Jinyintan Hospital showed that 36% of patients had elevated D-dimer, 16% showed a reduced aPTT, 6% showed an extended aPTT, 30% showed a shortened PT, and 30% showed an extended PT[87]. In a large meta-analysis of 7613 COVID-19 patients, it was found that in severe infection and non-survivors, the platelet count was lower, indicating that platelet counts may be a predictor of COVID-19 mortality[88,89]. COVID-19-associated thrombocytopenia primarily affects clot formation kinetics and clot strength on Quantra viscoelastic analysis; however, the details of *in vivo* fibrinolysis in COVID-19 have not yet been thoroughly investigated[89].

A retrospective analysis of the routine coagulation parameters of 183 patients with COVID-19 revealed that plasma FDP and D-dimer in non-survivors were significantly above those in survivors; PT and aPTT were also significantly prolonged[39]. A retrospective analysis of 138 COVID-19 patients confirmed that D-dimers increased after admission[90]. Previous studies have shown that elevated D-dimer is an independent risk factor for ARDS and mortality in COVID-19 patients[91].

COVID-19 infection has a significantly elevated vWF level together with increased FVIII clotting activity; this likely reflects the combined effect of the more significant release of Weibel-Palade bodies from endothelial cells and the acute-phase reaction. Meanwhile, ADAMTS13 activity was found to be mildly to moderately reduced in COVID-19 patients[75,92,93]. Fibrinogen level is increased to 5.0–7.0 g/dL on average for COVID-19-infected patients, CRP is also increased as an acute-phase reactant associated with elevated IL-6[94,95]. Meanwhile, antithrombin is consumed during coagulation, and the mild antithrombin deficiency occurs in COVID-19 infection whereas protein C has not been decreased in any of the patients assessed[96]. Mildly prolonged aPTT clotting times have been reported in some COVID-19 patients, indicating a prothrombotic state[96].

In a series of 24 intubated patients with severe COVID-19 pneumonia, PT and aPTT were either normal or slightly prolonged, platelet counts were normal or increased (mean, 348000/mL), fibrinogen increased (mean, 680 mg/dL; range 234 to 1344), D-dimer increased (mean, 4877 ng/mL; range, 1197 to 16954), factor VIII activity increased (mean, 297 units/dL), vWF antigen significantly increased (mean, 529; range 210 to 863), *per* endothelial injury. A slight decline in antithrombin and free protein S, with a slight increase in protein C, were also reported. Regarding TEG, there was shortening in reaction time (R) in 50% of patients and in clot formation time (K) in 83% of patients. There was an increase in maximum amplitude in 83% of patients, and also a reduction in clot lysis (LY30) in 100% of patients. Other studies have reported similar hypercoagulable states, including very high D-dimer, vWF antigen and activity, and factor VIII activity[43,97]. Two studies showed a high rate of lupus anticoagulant in patients with prolonged aPTT [50 of 57 tested individuals (88%) and 31 of 34 tested individuals (91%)] [42]. Another study reported 3 cases with severe COVID-19 and cerebral infarction, one with bilateral limb ischemia, within the setting of elevated antiphospholipid antibodies. Whether antiphospholipid antibodies play a significant role in the pathophysiology of thrombosis related to COVID-19 requires further investigation[41]. DIC manifests as coagulation failure and an intermediate phase within the development of multiple organ failure, which is common in many critically ill patients[98]. Tang *et al*[25] recently assessed 183 patients with COVID-19, of whom 21 (11.5%) died. The primary common differences between those who died and survivors were the increased levels of D-dimer and FDPs (an approximate 3.5- and approximately 1.9-fold increase, respectively) and PT prolongation (by 14%, $P < 0.001$), 71% of these patients who died fulfilled the International Society on Thrombosis and Hemostasis (ISTH) criteria for DIC compared with only 0.6% among survivors[40,99]. The COVID-19-related hypercoagulable state has been described as a DIC-like state, especially because many affected individuals are acutely ill and meet the criteria for probable DIC in the ISTH scoring system[99]. However, the main clinical finding in COVID-19 is thrombosis, whereas the main finding in acute decompensated DIC is bleeding. COVID-19 has similar laboratory findings of DIC, including elevated D-dimer and thrombocytopenia in some patients. However, in COVID-19, there is high fibrinogen and high factor VIII activity which are not found in DIC[40,99]. According to the recommendations from ISTH, the American Society of Hematology (ASH), and also the American College of Cardiology, routine testing for inpatients should include complete blood count, coagulation studies (PT and aPTT), fibrinogen, and D-dimer, and it will be repeated according to the clinical situation[100]. According to the American Society of Hematology recommendations regarding the diagnosis of PE, a normal D-dimer is sufficient to exclude the diagnosis of PE. In patients with suspected PE because of unexplained hypotension, tachycardia, worsening respiratory status, or other risk factors for thrombosis, computed tomography with pulmonary angiography (CTPA) is the preferred test. Ventilation/perfusion (V/Q) scan is an alternative if CTPA cannot be performed or is inconclusive, although the V/Q scan is also unhelpful in individuals with significant pulmonary involvement from COVID-19[101]. To date, whether these hemostatic changes are characteristic for SARS-CoV-2 or are an element of cytokine storm, as observed in other viral diseases, is unknown[102,103].

Regarding COVID-19 induced coagulopathy, we conclude that it meets the criteria of sepsis-induced coagulopathy (SIC), defined as a reduced platelet count, increased INR, and higher organ dysfunction score[40,104]. Table 2 shows the various laboratory parameters altered in SARS-CoV-2 and their implications in COVID-19 severity[105,106].

MANAGEMENT STRATEGIES

The cumulative incidence of COVID-19-associated VTE risk has raised concerns. Table 3 shows the frequency of venous thromboembolic complications in COVID-19 patients in different studies[64,107,108].

Many international societies and ministries of health have to publish their interim guidance to overcome this challenging situation[49,65,109-111]

Table 2 Various laboratory parameters that are altered in severe acute respiratory syndrome coronavirus 2 and their implications in coronavirus disease 2019 severity

Clinical index	Alterations with COVID-19 severity	Ref.
Neutrophil-to-lymphocyte ratio	Increased	[84,122-124,131,134-136]
CRP	Increased	[122,124,125,128,129,131,134-136,137-144]
Platelets	Decreased	[78,83,122,126,129,131-133,136,145,146]
Lymphocytes	Decreased	[78,128,129,131,134-136,147,148]
D-dimer	Increased	[55,83,84,127,128,131,137,144-146,149-152]
Ferritin	Increased	[91,94,128,129,131,134,135,137-139,144,153-155]
Procalcitonin	Increased	[83,84,128,144,156-158]
Lactate dehydrogenase	Increased	[106,129-131,152,159-173]
Albumin	Decreased	[111,116,128,129,136,148,174-186]

COVID-19: Coronavirus disease 2019; CRP: C-reactive protein.

Table 3 Frequency of venous thromboembolic complications in coronavirus disease 2019 patients

Ref.	Proportion	Cumulative incidence	Median follow-up	Patients
Cui *et al*[59]	20/81 (25%)	NR	NR	ICU patients
Klok *et al*[60]	68/184 (37%)	57% or 49% adjusted for competing risk of death	14 d	ICU patients only.19 PE were limited to subsegmental arteries.65/68 venous events were PE (95.6%)
Poissy *et al*[61]	VTE 22.2% of 54 ICU admitted			
Helms *et al*[44]	27/150 (18%)	NR	NR	ICU patients with ARDS 25/27 events were PE (92.5%)
Poissy *et al*[61]	PE only 22/107 (20.6%)	20.4% calculated at ICU day 15	6 d	ICU only
Middeldorp *et al*[63]	Venous thromboembolism 39% of COVID-19 ICU cases 74 patients			
Llitjos *et al*[64]	DVT: 18/26 (69%); PE: 6/26 (23%)	NR	NR	ICU patients. Systematic ultrasound screening
Léonard-Lorant *et al*[183]	PE only 32/106 (30%)	NR	NR	24/32 (75%) PE-positive patients were in the ICU
Grillet *et al*[184]	PE only 23/100 (23%)	NR	NR	Ward: 6/61 (9.8%); ICU: 17/39 (43.6%)
Middeldorp *et al*[63]	33/198 (17%)	15% at 7 d; 34% at 14 d	5 d	Ward: 4/123 (3.3%); ICU: 35/75 (47%); 11 (5.4%) clots detected on screening 11/33 events were PE (33%)
Lodigiani *et al*[185]	16/362 (4.4%)	21% (time not reported)	10 d	ICU 4/48(8.3%); Ward 12/314 (3.8%)
Thomas *et al*[186]	6/63 (9%)	27%	8 d	ICU patients
Cattaneo *et al*[108]	DVT only 0/388 (0%)	NR	NR	Non-ICU Ward 64 patients had screening ultrasound. All negative

DVT: Deep vein thrombosis; ICU: Intensive care unit; NR: Not reported; PE: Pulmonary embolism.

Although the general adoption of many societies[112] of the interim guidance of the ISTH[110], some institutions may vary in their management strategy of thromboembolic complications and would encourage enrollment in clinical trials to determine the best approach[113,114]. The ISTH recommends that all inpatients (ICU, medical non-ICU, and perioperative surgical and obstetric patients with COVID-19) receive prophylactic anticoagulation unless contraindicated after careful stratification with a DIC score. The low prophylactic dose molecular weight (LMW) heparin is preferred [*e.g.*, enoxaparin in a dose of 40 mg to 60 mg once daily for patients with creatinine clearance (CrCl) > 30 mL/min, and 30

mg once daily for patients with CrCl 15 to 30 mL/min]. Dalteparin, nadroparin, and tinzaparin are also recommended. In a retrospective study of 449 patients with severe COVID-19, 99 patients who received enoxaparin in prophylactic doses showed a better prognosis concerning mortality, especially those with high SIC score and markedly elevated D-dimer[115]. Moreover, LMWH could have anti-inflammatory properties that would help in COVID-19 patients where proinflammatory cytokines are markedly elevated[116]. The high incidence (43%) of VTE reported in a multicenter prospective study of ICU patients, mainly PE, despite being on a regular prophylactic dose of LMWH[43], prompted many experts to suggest higher doses and call for more aggressive anticoagulation with intermediate-dose or even therapeutic dose anticoagulation for thromboprophylaxis. For patients with CrCl < 15 mL/min or renal replacement therapy, unfractionated heparin can be used. Doses should be modified according to weight and pregnancy conditions. Full-dose anticoagulation is indicated in those with documented VTE like DVT or PE in the same way as those without COVID-19 infection.

Not all patients have access to confirmatory tests for VTE in real life. The empirical initiation on full-dose anticoagulation can be justified by the local consultation of expertise in hemostasis and thrombosis and clinical evaluation of individual patients. Sudden respiratory status deterioration in a previously stable intubated patient not explained by a cardiac cause indicates a high suspicion of PE. Moreover, those with highly elevated fibrinogen and/or D-dimer and otherwise unexplained respiratory failure, superficial thrombophlebitis, retiform purpura, recurrent clotting of arterial lines, or central venous catheters despite prophylactic anticoagulation are highly indicated for full-dose anticoagulation. The dose dilemma for critically ill ICU COVID-19 patients is still not resolved. Whether the regular prophylactic, intermediate, or therapeutic dose would better treat disease morbidity and mortality needs future clinical trials to improve our practice. This strategy is supported by the American Society of Hematology, which recommends against empiric full-dose anticoagulation because of the increased risk of bleeding in the same setting of VTE with this approach[55]. Tissue plasminogen activator (tPA) is suitable for use in its known indications, *e.g.*, massive limb DVT, extensive PE, acute cerebrovascular stroke, and acute myocardial infarction. TPA use was described in a case series of three advanced COVID-19 patients with ARDS that improved their respiratory status and laboratory parameters[117]. Of note, all patients with proven VTE must be maintained on anticoagulation for at least 3 mo after discharge. Immobility, old age, recent surgery, and other risk factors for thrombosis should be considered before deciding thromboprophylaxis in outpatients with COVID-19 with close observation. Patients undergoing clinical trials for COVID-19 new therapeutic options should be closely monitored for possible drug-drug interactions with thromboprophylaxis treatment. The British Thoracic Society recommends therapeutic LMWH for inpatients with COVID-19 disease who are managed on general wards and require supplemental oxygen.

In contrast, the patients with no evidence of VTE or other indication for therapeutic anticoagulation who require high-flow oxygen, CPAP, NIV for severe ventilatory failure, or invasive ventilation should receive less than therapeutic dosing[118]. Meanwhile, The Italian Society of Thrombosis and Hemostasis strongly recommends prophylactic anticoagulation with LMWH, UFH, or fondaparinux for the entire hospital stay for 7–14 d more after hospital discharge[119]. Furthermore, the American College of Chest Physicians and Global COVID-19 Thrombosis Collaborative Group recommends standard dose anticoagulation for inpatients with COVID-19 disease and ICU/Critical Care patients; meanwhile, SIGN and NICE NG-191 exerts intermediate-dose/ standard dose anticoagulation for those patients[120-122].

Much International and National guidance regarding VTE thromboprophylaxis has been published; however, more extensive studies are required to investigate the potential therapeutic approach. Most of the international guidelines and recommendations (ISTH-IG, ACF, CDC, and ASH) adopt stopping anticoagulation in patients who developed bleeding or severely thrombocytopenic; furthermore, they also do not recommend a particular platelet count threshold[123]. Furthermore, the expert panel reports by CHEST/AIPPD/AABIP stated that empiric use of therapeutic anticoagulation regimens in ICU patients with COVID-19 is not beneficial and may be harmful, while its use in hospitalized, noncritically ill patients with COVID-19 remains uncertain[123].

OUTCOME AND PROGNOSIS

The catastrophic event of unopposed coagulopathy and DIC is a strong predictor of mortality in patients with COVID-19. On a laboratory basis, a significant elevation in D-dimer and INR with a decrease in fibrinogen level was also observed in non-survivors at days 10-14, and this was considered a poor prognostic sign[55]. For this reason, continuous and close monitoring of their levels is essential to determine prognosis and outcome, D-dimer level above 1 μg/mL was a strong and independent risk factor for death in this population[124]. In an observational study, a mean D-dimer level of 2.12 mg/L was observed in patients who did not survive compared to a concentration of 0.61 mg/L in survivors [55]. Another study revealed that patients admitted to ICU had significantly higher median D-dimer concentrations than patients who did not receive ICU care[84]. A third study reported that D-dimer on admission greater than 1 mg/L resulted in an 18-times increased risk of death[125]. These data provided strong evidence that D-dimer could be used as an excellent prognostic sign[125]. A retrospective study

that included 449 patients admitted to the hospital with severe COVID-19 infection showed that the use of prophylactic heparin was associated with a lower mortality rate than in patients who did not receive prophylactic heparin[115]. The available data about coagulopathy in COVID-19 patients suggest that regular monitoring of PT, platelet count, and D-dimer concentrations could predict prognosis and expected complications. Accordingly, there is justifying evidence supporting using a prophylactic dose of LMWH to prevent VTE in critically ill COVID-19 patients[126].

COVID-19 AND BLEEDING

Indeed SARS-CoV-2 is not as pathogenic as other RNA viruses (Ebola and hemorrhagic fever viruses) in causing severe hemorrhagic manifestations[127]. Owing to the abnormal coagulation cascade and subsequent high risk of thrombosis necessitating pharmacologic VTE prophylaxis, especially in severe COVID-19, the risk of bleeding with COVID-19 due to over anticoagulation, SIC, or DIC is inevitable. Although there are few reported data about clinically-overt bleeding in the setting of COVID-19, close observation for the occurrence of bleeding or thrombosis is mandatory for all COVID-19 patients who develop SIC or DIC[128]. In the absence of overt bleeding, the correction of coagulopathy is not mandatory in most COVID-19 patients. It is recommended to monitor full blood count, coagulation profile, and/or TEG and Rotational Thromboelastometry are all needed in cases of minor bleeding. However, in cases of significant bleeding as observed with a decrease in systolic blood pressure to less than 90 mmHg and/or increase of heart rate more than 110 beats *per* minute, management should be started immediately with FFP (15-25 mg/kg if PT/INR or aPTT ratios are greater than 1.5), platelet transfusion (for platelet count < 50 × 10^9/L), fibrinogen replacement (when fibrinogen level is < 1.5 g/L).

Additionally, prothrombin complex concentrate will be given if FFP transfusion is not feasible and/or tranexamic acid (in a dose of 1 g over 10 mi) followed by a further dose (of 1 gm) if bleeding persists or restarts in the following 24 h provided that the patient does not have any evidence of DIC and followed by repeated monitoring with coagulation screens[129]. In a unique observation from Thailand on 41 COVID-19 infected patients initially presented with bleeding and petechiae, no specific additional treatment for this hemorrhagic problem was needed, and fortunately, no deaths occurred. This study and other studies may be of great value to raise awareness about the hemorrhagic presentation associated with COVID-19. Therefore, investigation and follow-up for possible hemorrhagic problems induced by COVID-19 are highly recommended[130]. A retrospective study comparing the risk of thrombosis *vs* the risk of bleeding in COVID-19 patients showed that critically ill patients had an increased incidence of bleeding (26.7%). This was a complicated situation in the setting of VTE prophylaxis and could be explained by dysregulated hemostasis in severe COVID-19. However, in noncritically ill COVID-19 patients, the prediction risk of VTE and major bleeding was minor. Based on that, critically ill COVID-19 patients are predisposed to both high risk of thrombosis and bleeding, so prevention strategies should be individualized according to the assessment of thrombosis *vs* bleeding risk[131]. Another study reported two cases of a significant hemorrhagic complication in severe COVID-19 patients presented by spontaneous abdominal, internal bleeding. Patients had bilateral interstitial pneumonia, and there were no other apparent predisposing factors for bleeding. Patients were managed with interventional radiology, with no mortalities recorded. These imbalances (or disruption) in platelet production and disorders of the coagulation system induced by SARS-CoV-2 need to be further clarified in extensive prospective studies[132]. Only a few published data about COVID-19 infection with known bleeding disorder patients are available. A case report of mild COVID-19 in a known hemophilia-A patient reported no evidence of bleeding linked to COVID-19 infection, and the patient recovered completely with only home isolation, antiviral agents, empirical antibiotics, and supportive therapies. Indeed, mild COVID-19 is not known to increase the risk of bleeding, even in patients with known bleeding disorders[133]. Transfusion therapy should be restricted for those with active bleeding, requiring an invasive procedure, or at otherwise high risk for bleeding complications and accordingly to be managed similar to those in ISTH guidelines for DIC[134].

CONCLUSION

In conclusion, and based on all the previously discussed data, we should highlight the importance of using empirical therapeutic anticoagulation for COVID-19 patients to guard against possible thromboembolic events with close observation for the occurrence of bleeding.

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REVIEW

Syndemic aspects between COVID-19 pandemic and social inequalities

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Abstract

Although the coronavirus disease 2019 (COVID-19) pandemic has reached all over the world population, it has demonstrated a heterogeneous impact on different populations. The most vulnerable communities which coexist daily with the social inequalities like low access to hygiene and personal protection products, crowded residences, and higher levels of chronic diseases have a higher risk of contact and the spread of infection, beyond unfavorable clinical outcomes. The elevation of the risk of infection exposure can be related to gender due to the presence of a larger contingent of women in essential services, as well as frontline and cleaning professionals who regardless of gender have the greatest exposure to the virus. Such exposures can contribute to the development of fear of contaminating themselves or their family members associated also with the work stress, both of which are related to the emergence of mental disturbances in these populations. Furthermore, conditions of unsanitary living and low socioeconomic status, populations at war, pre-existing social barriers, and ethnicity have contributed to more impact of the pandemic both in the exposure to the virus and access to health services, COVID-19 management, and management of other pathologies. At the same time, factors such as the closing of non-essential services, the loss of jobs, and the increase in household spending aggravated the social vulnerabilities and impacted the family economy. Lastly, the COVID-19 pandemic contributed still more to the impact on women's health since it propitiated a favorable environment for increasing domestic violence rates, through the segregation of women from social life, and increasing the time of the victims with their

aggressors.

Key Words: COVID-19; Minority groups; Pandemic; Social inequalities; Socioeconomic factors

Core Tip: The social inequalities interact continuously with the coronavirus disease 2019 pandemic, influencing the development and heterogeneity of the disease while they are potentiated by the pandemic context. Therefore, understanding the individual features of each group is of fundamental importance to the compression of the illness risk, morbidity, and mortality of the infection, data that can be used to create specific measures for health prevention and recovery of the population.

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INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), had its first case in Wuhan, China in 2019, quickly spreading to other countries[1-3]. This virus colonizes the respiratory tract causing, normally, mild symptoms such as cough, fever, dyspnea, sputum, and sneezing. Severe cases of cardiac damage, shock, kidney, and respiratory failure can occur, mainly in individuals with pre-existing chronic diseases[4,5].

On the other hand, the severity of the disease can also be influenced by the social context in which the person is inserted since unique features of each population can propitiate the elevation of the risk of contagion and increase the morbimortality of the infection[6]. Studies have demonstrated that during the pandemic, the social inequalities have been responsible for aggravating the damages caused by COVID-19[7]. Therefore, in addition to considering the biological characteristics of the virus and individual, it is also essential to evaluate the functional vulnerabilities of the population such as the necessity to exercise the work activity during the lockdown because both are important predictors of the illness risk[8].

Thus, although the COVID-19 pandemic has affected the world, its dissemination and impact on the health of different social groups have been demonstrated not to be homogeneous[9]. Access to health information, different age groups, gender, minority groups, socioeconomic and schooling levels[10], inadequate housing quality, absence of potable water and electricity, overcrowding, and bad sanitary conditions can influence the infection heterogeneity[11]. Such conditions are visualized in populations that daily coexist with armed conflicts, in regions historically more vulnerable with low access to health services, provisions, high rates of infectious and chronic diseases, and factors able to add to the COVID-19 pandemic and potentiate its impact on health[12].

Besides the grievances on population health, the proper pandemic also significantly influences the increase of these inequalities[7], reverberating also on the world and family economy. Data from 2020 demonstrate that during this period, there was increasing poverty and hunger, and jobs were lost with an approximate mark of 400 million, beyond the reduction in the workers' income worldwide[13]. The lockdown, although it has been an effective measure to control the spread of COVID-19, also contributed to negative impacts on family economy through the closing of some non-essential services, an increase in the unemployment rates, and the impossibility of going to work while there was an increase of household expenses with personal entertainment, toiletries, cleaning products, and face masks and gloves[14]. Although such misfortunes can reach all the population, they affect with more intensity the populations more vulnerable and with a low socioeconomic level, contributing to the increase of socioeconomic fragility of these groups[15]. Besides that, both the prioritization of essential or non-essential services and the contagion fear resulted in the reduction of access and seeking for health services such as sexual and mental health and oncology, influencing the increase of the vulnerability of these populations[16].

Lastly, although masked by the impacts of the pandemic, domestic violence emerges as an important aggravating factor for women's health in the current times[17]. The lockdown made possible a greater psychological and financial domain of abusers on their victims while making it difficult for these women to seek help[18]. This exposure to violence was related to the elevation of the risk of death and suicide in females, as well as the development of mental disturbances such as post-traumatic stress

disorder, anxiety, and depression[17]. Table 1 synthesizes the relation between the individual characteristics of the populations and the impacts of the COVID-19 pandemic.

The present article aims to evaluate the socioeconomic aspects that permeate the COVID-19 pandemic and how these influence the disease.

METHODOLOGY

The present minireview was based on the articles published in the United States National Library of Medicine (PubMed), which were searched using the following descriptors: COVID-19; SARS-CoV-2; gender; pandemic; disparity; chronic diseases; inequalities; socioeconomic; race; ethnicity; home working; social impact; social distancing; essential services; unemployment rate; domestic violence; vaccine; war situation; and indigenous people. Initially, 5908 articles were found. The inclusion criteria encompassed articles that presented the descriptors in their title or abstract, and manuscripts were written in the last 10 years in the English language. Paid manuscripts, articles not available in full text, and texts that do not address the research topic were considered the exclusion criteria. Lastly, the repeated articles were excluded and 136 were used in the construction of this minireview.

MINORITY GROUPS DURING THE PANDEMIC

The concept of ecopandemic injustice, which seeks to explain the interrelations between pandemic and ecological systems, demonstrates how COVID-19 reveals and deepens the structural inequalities that are formed along the lines of environmental health[19]. Some individual features such as gender, socioeconomic conditions, and ethnicity play a major role in COVID-19 susceptibility and progression, leading to a higher risk of infection, mortality, and hospitalization in the most vulnerable groups[20-22]. On the other hand, the global crisis triggered by the pandemic made the links between racism, poverty, and health more visible and exacerbated[19,23].

Gender

Although men and women are equally susceptible to COVID-19, studies demonstrated that the rates of fatality and admission to the intensive care units (ICUs) are higher in males[20,24,25]. Hypotheses such as the differences in the angiotensin-converting enzyme 2 (ACE2) expression between genders seek to explain these sex disparities[24,25]. Many studies have shown that ACE2 expression is higher in males than in females, probably due to differences in sex hormone activity[20,25,26], since estrogen may present a regulatory effect on ACE2, controlling its expression in human bronchial epithelial cells[26,27]. Besides that, the transmembrane protease serine 2 (TMPRSS2), an enzyme necessary for the priming of the viral S protein and for spreading the virus in the body[26], suffers from the influence of androgen receptors (ARs), higher expressed in males due to the presence of dihydrotestosterone and acting in the transcription of TMPRSS2[24,26]. Lastly, behavioral and underlying comorbidity differences, such as alcoholism, smoking, and hypertension, are higher among men than women and contribute to the gender gaps in COVID-19 mortality[20,28].

Nevertheless, the women face secondary effects of the pandemic that place them in a vulnerable condition. The female gender represents most of the essential care employees such as frontline health care professionals[20,29], laundry and cleaning staff, administrative assistants working in hospitals, social workers, cashiers, and food service workers. Their close physical proximity to the population in general and high interaction with others contribute to increasing the risk of exposure and infection[20,30,31], which also can elevate the hospitalization and death risk[32]. In addition, pregnant women are considered one of the most vulnerable groups regarding COVID-19[33], because they present a greater risk of developing severe complications in respiratory infections. On the other hand, these individuals must continue with prenatal care appointments, which may increase the risk of exposure to the virus[33,34]. Studies have reported that the crowded hospitals and staff and supply shortages may affect the quality of care and increase the risk of obstetrics complications[33]. Lastly, life-saving treatments and vaccines may be denied or hampered to pregnant women due to a lack of data or concern for fetal safety [34,35].

Socioeconomic conditions

Lower socioeconomic status has been related to higher SARS-CoV-2 infection rates and worse clinical outcomes[36-38]. Such facts can be explained by delay in seeking help in COVID-19 cases[37] and higher rates of comorbidities, such as cardiovascular diseases, diabetes, and cancer in the most vulnerable populations[21,39]. In addition, the use of public transportation, lack of adequate personal protective equipment, poor general health and nutritional status, housing conditions, living in poverty or deprivation, lack of insurance, household overcrowding, lower level of education, speaking in a language other than the national language in a country, being an immigrant, and unemployment are

Table 1 Relation between individual characteristics and the coronavirus disease 2019 pandemic

Individual characteristic	Risk factors	Repercussion
Gender	Higher expression of ACE2 and ARs in males[20,25,26]	Higher mortality among men[20,28]
	Greater rates of alcoholism, smoking, and hypertension in men[20,28]	
	Women as most of the essential care employees[20,29]	Increased risk of exposure among women[20,31]
Socioeconomic conditions	Delay in seeking help and higher rates of comorbidities[37,39]	Higher infection rates and worse clinical outcomes[36,37]
	Use of public transportation, household overcrowding, lack of personal protective equipment, smoking, alcoholism, poor diet, and being an immigrant[36,37,40,41]	Higher exposure and mortality[36,37,40,41]
Ethnicity	High rates of comorbidities in the minority ethnic groups[51]	Risk of severe forms of COVID-19[22,45]
	Household crowding, language barriers, and difficulties in accessing healthcare systems[22,52]	Increased mortality for COVID-19[50]
	Usually workers in essential industries[51,52]	Higher exposure to the virus[51,52]
Health service accessibility	Resources reallocation to COVID-19 management[76]	Delay in the realization of elective surgeries[78]; reduction of managing chronic disease[84], services of sexual education[82] and family planning[79,82,83]
	High cost of vaccines against COVID-19[92] and discrepancies in the immunization strategies[93]	Reduction of the vaccine access, increase in the infection and death rates[92,93]
	Language Barriers[97]	Low knowledge about the vaccination process[97]
	Mistrust with the health systems[95,96], immigrants with pending documentation, negativism, and having to work during the vaccination process[94]	Reduction of vaccine access by minority groups[94,96,97]
Labor vulnerability	Frontline or essential work[100]	Higher exposition rates, sleep disturbances, suicide anxiety, depression, PTSD[104]
	Marginalized population, low level education[99], and lockdown policies[104]	Unemployment, reduced family income, food insecurity[98]
	Work at home[116]	Sedentary lifestyle, risk of cardiovascular events[115,117]
Domestic violence	Less social interaction and opportunities for denouncing, and socioeconomic problems[119,125]	Physical and psychological consequences (anxiety, depression, and stress)[132]

COVID-19: Coronavirus disease 2019; ACE2: Angiotensin-converting enzyme 2; ARs: Androgen receptors; PTSD: Post-traumatic stress disorder.

factors that may increase the exposure to and mortality of COVID-19[36,37,40,41].

In association with the aforementioned, lower education levels and lack of information may influence lifestyle and behavior, leading to habits such as smoking, drinking, and poor diet, which are risk factors for severe forms of COVID-19[40]. People with lower education levels tend to work in jobs that do not offer the opportunity to work remotely, increasing the exposure risk[39]. Correspondingly, one study conducted in Spain in 2021 reported that workers with low salaries, unemployed, and people on minimum integration income had an increased probability to contract COVID-19 than workers with salaries equal to or higher than €18000 per year[42]. In this context, in certain communities, social distancing is an inaccessible privilege, because it is impossible to depart from work for the period necessary to carry out quarantine[23,43]. Similarly, homeless people, displaced populations, and prisoners cannot choose to be physically distant from each other, which impairs the realization of isolation[43].

On the other hand, past evidence and experience suggest that marginalized and low-income communities suffer the greatest impact from the current pandemic, since they have health systems historically fragile, overloaded, and with few resources. Therefore, it is clear that COVID-19 shows disparities in several areas, particularly the potentially serious healthcare discrepancies[23,43]. Consistent with this, although medical advice is the adoption of safe practices which include hand hygiene and the use of masks in public environments[23], the water insecurity, and lack of access to basic sanitation and hygiene products in many parts of the world[42] create a new barrier for certain marginalized groups[23]. Such facts are corroborated by current data suggesting that 1 in 4 people of the global population do not have access to clean water or soap to wash their hands at home[44].

Ethnicity

The racial/ethnic minority population also face gaps and disparities in the COVID-19 pandemic[22,45]. In a systematic review conducted with 52 studies, 11 reported that racial/ethnic minority groups were at higher risk of exposure to COVID-19 when compared to the White population and 11 studies demonstrated an increased risk of death for these minority groups[40]. Data from National Center for Health Statistics report that Hispanic populations represent approximately 21% of excess deaths[45], which is related to another study that reported a two times higher risk of Hispanics dying from COVID-19 than Whites[45]. This research also demonstrated that American/Black and Hispanic populations present an increased risk of contracting COVID-19 and similar rates of case fatality[46].

The disparity in the consequences of the pandemic among ethnic groups is so evident that The Washington Post revealed in one of its articles that African-American people are contracting SARS-CoV-2 at higher rates and are more likely to die[23]. The Centers for Disease Control and Prevention's Morbidity and Mortality Weekly Report (MMWR) reported that the Black population is disproportionately affected by COVID-19, accounting for 33.1% of hospitalizations for the disease, despite representing only 18% of the population in the area analyzed[47]. Similarly, data from the Johns Hopkins University and American Community Survey revealed that the infection rate is 3 times higher and the mortality rate is 6 times higher in municipalities with a predominance of Black residents when compared to those with White predominance[23]. Such data correspond to the findings of other studies that described that regions where the Black population was present in an above-average proportion also had higher rates of cases, moderated by social segregation[48], and deaths from COVID-19[49].

Some hypotheses such as the greater burden of obesity and other comorbidities in the minority ethnic groups[50], along with ethnic differences in economic status, the density of residence, household crowding[22,51], language, and other structural barriers to accessing healthcare systems would be related to the increased mortality for COVID-19 in this population[50]. Furthermore, minority ethnic groups are usually employed in essential industries, which do not provide opportunities for working from home, leading to closer proximity with other individuals and higher exposure to the virus[51,52].

Similarly, COVID-19 also impacted the health of approximately 900000 indigenous people (IP) in Brazil. Even if part of this population lives in native lands, theoretically more isolated from society in general, the interaction is inevitable. The first reported case in IP occurred on April 9, 2020 in the Kokama tribe after contact with an infected doctor. As of June 5, there were already 70 deaths in patients aged between 0 and 88 years. Among the victims were the so-called Caciques, a title bestowed on the oldest and leader of the tribe. These deaths can mean an irreparable loss for the maintenance of the culture and traditions of these people[53]. The invasion of protected lands by illegal activities such as mining, drug trafficking, and logging, as well as tourists, missionaries, and traders, are other means of contact between IP and infected people[54].

An ecological study, using spatial analysis techniques and government databases, carried out between March 24 and October 26, 2020, revealed the occurrence of 32024 cases and 472 deaths from COVID-19 in IP, with approximately 85% of the fatal cases occurring in individuals over 50 years old, mainly in the north and midwest regions of Brazil. This study also calculated the mortality rate of COVID-19 in IP at 265.37 deaths per 100000 inhabitants, against 41.1 deaths per 100000 inhabitants in the general population[55]. There are some possible explanations for this higher rate in IP, among which are the high prevalence of comorbidities such as obesity, hypertension, diabetes mellitus, and malnutrition, in addition to the low access to health services, potable drinking water, and good sanitary conditions of housing or even soap and alcohol gel[53,54].

To reinforce the vulnerability of IP, another retrospective study identified that the excess of deaths in the general Brazilian population in 2020 showed an increase of 18.1% in relation to the expected value, while in IP this growth was substantially higher, at 34.8%. It is worth noting that this excess of deaths is directly related to the fatal cases of COVID-19[56]. This scenario can be even more serious as studies also raise the possibility of under-reported cases of COVID-19, leading to the belief that these rates may have been higher[57,58], and even leading to the possibility of risk of the decimation of the entire indigenous villages in the southern region of the country[59].

The world perspective on the COVID-19 pandemic and IP is not very different from what happens in Brazil. The difficulties in dealing with COVID-19 are closely related to limited state and federal assistance and this is a reality for IP in different parts of the world[60]. A recent study looked at differences in stress, anxiety, and depression experienced by different ethnic groups during the COVID-19 pandemic. Their results demonstrated that indigenous ethnicity is a specific risk factor for the psychiatric disorders studied and suggested that greater attention to the mental health of this population is needed[61]. In addition, the socioeconomic marginalization and the social inequalities that affect with more severity the indigenous communities and potentiate the pandemic effects in these populations around the world[62] also can hinder these populations' access to vaccination[63].

COVID-19 PANDEMIC AND WAR STRESS

Syria and Lebanon are Middle Eastern countries that have been living with internal armed conflict for

about 11 years since the Arab uprising in 2011. This reality of combat and altercation generated, in addition to an undeniable and expressive number of deaths and injuries, the population displacement and collapse of health systems[64]. With the emergence of the COVID-19pandemic, the situation of poor health in these places has become even more evident, given that if even countries with health systems and more advanced resources struggled with difficulties to fight COVID-19, those affected by conflicts ended up facing even more devastating outbreaks of the disease[65]. Yet, statements from several international public entities, such as the International Crisis Group, warned of concerns about these locations, where the already challenge of global health was met with wars and political conditions that generate an extremely weak health system, mass displacement, and lack of basic infrastructure, resulting in more impacts of the COVID-19 pandemic[65].

There are several factors that put the Syrian population, of about 3.5 million people, at greater risk than the others in the face of the current global health condition. In addition to the presence of more than 2.8 million internally displaced people, this could be a potential route for the spread of the virus and an increase in the number of cases of the disease, as well as overcrowding of urban centers and rural areas, and the existence of more than 500 concentration camps arbitrarily built in the region[65]. Finally, the high rate of extreme poverty – estimated to be that about 83% of Syrians live below the poverty line – added to the inability of the Syrian health system, shaken and weakened by the 9 years of armed conflict, end up contributing to a lack of adequate and sufficient resources and supplies[66].

Thereby, unequal distribution of wealth, sociopolitical instability, and underreporting result in several COVID-19 incidences[67]. The first case of SARS-CoV-2 infection in Lebanon was confirmed in February 2020; since then, the case numbers have increased. However, it remains limited due to national confinement, closed borders, and care measures. Nevertheless, since August 2020, with the explosion of the Beirut Port, there was a decline in socioeconomic status, reaching 534968 positive cases and 7569 deaths by May 2021[68]. Yet, the COVID-19 dissemination coincided with a period of political instability [69].

Focus on public health sectors preparing to meet the infected patients threatens the continuity of some basic services, besides the fear of getting the infection and obligatory reclusion, which has stopped many individuals from visiting the psychological support. Yet, the lockdown measures negatively affect the maintenance of millions of people and about 30% of young people in Lebanon are unemployed in this context[70]. Moreover, one of the most important psychological impacts of the infected or suspected patients was the prejudice and stigma of having the disease, among the front line professionals. Those in quarantine were more likely to be stigmatized and rejected[71].

However, when comparing mortality rates in Middle Eastern countries, including Syria and Lebanon, there are lower figures than, for example, those in Europe and the Americas[72]. Such an estimate could lead to the erroneous conclusion that the pandemic has hit countries in conflict less strongly, as their estimates are less alarming than global ones. However, the conclusion must be precisely inverse: Given an overloaded health system, unequal distribution of wealth, and lack of sociopolitical stability, there is a high number of undetected and unreported cases in this region, making official data not reflect reality [67,72].

Therefore, although politics and health are subjects sometimes seen as unrelated, the index of political stability can and should be used as a predictor of the management capacity of a pandemic[73]. Thus, in countries in a constant war situation, such as Syria and Lebanon, the position in the face of a global health problem is complex, since its inhabitants and political leaders must deal with the pandemic and the ongoing war, two serious obstacles, which add up to the death and invalidity numbers[74].

RESTRICTION TO HEALTH SERVICES ACCESSIBILITY

The primary objective of the health system in Brazil is to provide health services to the population, regardless of gender, age, race, ethnicity, religion, nationality, social class, sexual orientation, or political position, promote treatment, monitor diseases, minimize pain, whether physical or psychological and, when possible, promote the cure[75]. However, COVID-19 generated a growing additional demand in the public health system, mainly in the increase of ICU beds and mechanical ventilation devices, necessary measures for the treatment of contaminated people in moderate and severe states[76]. As elective operations resume, operating room (OR) access has become increasingly challenging because of the large backlog of cases. Before the pandemic, many hospitals were running their ORs at near capacity, leaving little room to accommodate additional surgeries and forcing scheduling delays as long as 20 mo. As a result, patients are facing mounting challenges to the receipt of timely surgical treatment as outpatients and inpatients[77].

The pandemic represents a barrier to access to health services since these are organized for priority care for potentially infected patients and with professionals away from care for various reasons, with an overload of the remaining. In addition, people avoid going to services, due to social distancing recommendations and fear of contamination[78-80]. Thus, Brazil faces some challenges in the battle against the COVID-19 pandemic, including the risks of cross-infection (community infection) increase in densely populated areas, and low access to health services in areas where the number of beds in ICUs is scarce and poorly distributed, mainly in states with a low population density[76,81].

Experience from past outbreaks indicates the need to pay attention to the potential effects of the COVID-19 pandemic on sexual health outcomes, both in the immediate and long term[80]. The greater risk of sexually transmitted infections during the pandemic for women in situations of domestic violence or other conditions of psychosocial risks, such as the use of alcohol or drugs, poverty, among other situations of vulnerability, also needs to be recognized and should be a priority for health services [81]. Attendance at family planning services has also dropped dramatically in different countries. The consequences can involve an increase in the number of unwanted pregnancies and unsafe abortions, as well as maternal and neonatal deaths, and an impact on sexually transmitted infections. The effects could linger during the recovery phase of the pandemic, hitting disadvantaged and neglected groups again and reversing gains made in recent decades[76,82,83].

The treatment and follow-up of chronic diseases also suffer the impact of the pandemic. A study showed that diabetes (38%) was the disease most affected by resource reallocation and prioritization to COVID-19, followed by chronic obstructive pulmonary disease (COPD, 9%), hypertension (8%), heart disease (7%), asthma (7%), cancer (6%), and depression (6%)[84]. Non-infectious chronic respiratory diseases such as obstructive sleep apnea, asthma, and COPD were also negatively impacted. Both diagnosis/treatment and follow-up have been compromised by a reduction of resources, lack of adherence to face-to-face care, and interruption of clinical trials with possible innovative therapies, and these events can have negative consequences in the medium and long term for patient survival[85]. Recently, another study demonstrated a reduction in hospital admission for cardiovascular disease at the beginning of the pandemic and another study reported a lower overall hospital mortality and higher out-of-hospital mortality for patients with cardiovascular disease during rigid periods of isolation compared to other times of the pandemic[86,87]. These studies raised the hypothesis that the changes and interference of the conditions generated by the pandemic in the treatment and monitoring of diseases may negatively affect patients with cardiovascular diseases not infected by SARS-CoV-2[88]. Furthermore, the pandemic has also significantly affected cancer patients. The allocation of resources to deal with patients positive for SARS-CoV-2 has led to a shortage of essential drugs for the care of cancer patients, given that the replacement of therapy is a complex condition and not always possible since the limitation in the treatment of cancer can be fatal[89]. In addition, the diagnosis of some types of cancer such as gastrointestinal cancer was compromised by the risk of infection of patients[90].

In addition to the aforementioned, the inequalities present in the immunization process have contributed to the harm to human health and postponed the pandemic end[91]. Research demonstrated that the cost of vaccines against the COVID-19 impeded the access and the immunization process of some countries which suffered from the economic impact of the pandemic, and the adaptation of their health systems to attend to the population with the disease[92]. Furthermore, the discrepancy between the high stimuli to the creation of vaccination strategies in developed countries like the United States of America (USA) which vaccinated over half of its the population until September 2021 and detriment to countries like India which vaccinated about 13% of the population in the same period, made possible that new infection waves formed in these last countries, increasing the infection and death rates and also propitiating the emergence of new virus variants[93].

Vaccine access also is affected by the way that the communities are structured, since the necessity to work during the vaccination periods, the mistrust of the health system, documents pending related to immigration, religious negativism, and political opposition are individual factors that have contributed to decreasing the vaccine access by Latin and Hispanic people in the USA[94]. Similarly, studies have demonstrated a greater hesitation to vaccination by the people belonging to minority groups, mainly the Black population in the United Kingdoms and the USA, which could be related to possible historic disbelief of these people about the health system due to events like the Tuskegee Experiment[95,96]. Furthermore, immigrant people can present a reduction in the seeking of immunization due to spatial barriers that restrict the mobility to the locals of vaccination and language barriers since not speaking the language of the countries where they live can reduce the access to information about the process of vaccination[97].

LABOR VULNERABILITY AND IMPACT ON THE FAMILY NUCLEUS

Exposure to infection caused by SARS-CoV-2 is directly related to the nature of people's profession. In this context, frontline work can be mentioned, such as the health area and certain essential industries, in which there is greater interaction with other individuals[52]. This scenario becomes more serious in places with a high population density, households with shared sanitation facilities, and ineffective health systems, as is common in poorer regions of developing countries[98]. Furthermore, the COVID-19 pandemic has not only affected infection and mortality rates. With the adoption of restrictive measures to control transmission in several countries in 2020, such as the closing of establishments considered non-essential and rules of social isolation, economic and social aspects were also influenced. Thus, several changes were noticed in work relationships that had consequences on income and family management[98,99].

Social isolation involves exceptions such as essential workers (EWs), which include healthcare professionals (HCP), individuals working in the food production and distribution, emergency and protection services, communications, information technology, logistics, and delivery services. These EWs vary according to regulations and local economy[100] and their contacts, which increase the contagion risk itself and to other people, need to be retained [101]. The recommendations include support work from home, face shield, and individual protection equipment (IPE) for functions where social distancing is not possible, workplace layout changes, and improved cleaning and disinfection. However, working from home is often not feasible[102]. Besides that, achieving a balance between the provision of essential health care and protection of the HCP against infection, mainly due to the deficiency of the IPE, is challenging for the frontline team[103]. Furthermore, the COVID-19 pandemic affects the mental health of work-people. Anxiety, depression, post-traumatic stress disorder (PTSD), and sleep disturbances are more often present in HCP on the frontline, migrant workers, and those in contact with the public, where job insecurity, long-term isolation, and uncertain future worsen the psychological condition[104]. A systematic review showed that a high proportion of the HCP experience elevated levels of anxiety, depression, and insomnia, being more prevalent in the nurse team when compared with physicians [105]. Yet, rates of suicide are reported in this population, due to the psychological pressure, loneliness, financial crisis, and fear of dying[106,107]. Another study that evaluated Spanish health professionals described that about 56.6% of workers presented with PTSD, 59.6% had anxiety, and 41.1% had emotional exhaustion[108]. Among Chinese physicians, 50.4% and 71.5% of the study participants reported depression and anguish, respectively[109].

On the other hand, the economical and productive consequences of the pandemic can also affect labor sectors, while some individuals were forced to stop their work activities due to lockdown policies or effective job loss[104]. A study reported that almost two-thirds of the participants had their family income reduced during the pandemic and approximately half of them had reduced work hours or lost their job due to COVID-19[110]. Yet, the Spanish population estimates an increase in the unemployment rate of 27.88%, mainly in service sectors[111]. A search performed in Hawaii showed that the interviewees reported having difficulties spending for essential items and expected problems to increase in the next 3 mo, such as paying for alimentation, rent, and car expenses, as well as utility bills, and mobile/internet costs[112]. Other data obtained in the USA showed that about 28% of respondents declared that school closures were a factor that affected the finances of low-income families, as children no longer received free or reduced-cost meals in schools[113]. Moreover, domestic work gains importance in pandemic scenarios due to the great demand for care for both children and the elderly, but their employment situation, exposure, and vulnerability affect most of these workers. Therefore, they are at serious risk of losing their jobs, beyond the contagion danger, family estrangement, and violence in the house[114].

Generally, families belonging to marginalized or low-income populations tend to suffer the most severe effects. In this way, existing inequities were further aggravated by COVID-19[99,113]. In Liberia, Africa, it was identified in a study that about 67% of participating families had reduced income due to the pandemic. This situation contributed to the fact that 68% of respondents only had food in stock for a week or less, and 35% reported that they had skipped a meal in the last 7 d[98]. A study in Indiana, USA found that 55% of participants were worried about their family finances because they had lost their jobs. Another factor involved in greater economic precariousness was education, with people who did not have a university degree having twice the risk of food insecurity compared to those who had any college degree, while those without complete high school were 4 times more likely[99].

Another relevant issue is that the COVID-19 pandemic accelerated the process of transitioning from face-to-face work to remote work at home, and this affected the health of individuals[115,116]. A survey carried out in Japan with company workers showed that the average number of days of working from home per week went from 0.2 in 2019 to 1.0 during the pandemic in 2020. In this context, there was an increase in sedentary lifestyle, with more time dedicated to activities such as sitting, watching TV, and using the PC. A sedentary lifestyle is a problem that increases the risk of chronic diseases and fatigue and reduces workers' productivity[115]. In Pittsburgh, USA, a survey was carried out to assess the consequences for desk workers, most of whom had to migrate to remote work. The results show that these people also had an increase in sedentary time on rest days, and worse sleep quality, in addition to a reduction in work-related health, such as loss of productivity, concentration, and personal satisfaction [116]. A study highlighted that in Italy, the number of people working from home rose from 4.6% in 2019 to 19.4% in the second quarter of 2020. The findings point to an increase in physical inactivity and a reduction in outdoor physical exercise, indicating that this increase may have been greater in people who lost their jobs compared to those who could keep them. Such a scenario, which, added to an increase in hours of working and the adoption of less healthy diets, can contribute to an increased risk of cardiovascular events, such as obesity and hypertension[117]. Thus, several studies reported that unemployment also contributes to mental health commitment, especially among young people[118, 119]. It is important to note that even with the end or loosening of restrictions on social isolation, it is very likely that most companies will opt for remote work, either by popularizing available technologies or by saving costs. Thus, the health problems related to a sedentary lifestyle caused by COVID-19 may persist beyond the pandemic, requiring a joint effort among families, companies, and governments to reduce these effects[116,117].

INCREASE IN DOMESTIC VIOLENCE IN THE FACE OF SOCIAL ISOLATION

Domestic violence is defined in The Protection of Women from Domestic Violence Act as "any act of commission or omission or conduct resulting in physical, verbal, emotional, sexual, and economic abuse"[82,120]. Especially during the first 6 mo of the pandemic, support mechanisms for victims of domestic violence such as specialized centers in Spain, Cyprus, Brazil, and the United Kingdom reported an increase of 20%, 30%, 40%-50%, and 25%, respectively, in complaints. Furthermore, Google's search engine detected an elevation of about 75% in searches related to supporting domestic violence [121-123]. It is possible to observe a trend already experienced in other moments of the crisis, in which, as in the current pandemic, there were mainly economic and social problems, linked to the loss of jobs, reduction of family income, food insecurity, stress, reduced interactions and social support, and increase in the consumption of alcoholic beverages and drugs, which corroborate the increase in violence rates [124,125].

The measures of confinement and social isolation restricted contact with external family members, neighbors, and co-workers, which makes it difficult to search for help or the opportunity to talk about the violence faced at home[126,127]. Isolation has made it more complicated for the victim to denounce her aggressor since she is confined with him[128,129], as well as made access to social services and health services and assistance to the population more difficult[129]. Therefore, in a situation of aggression, in addition to the violence suffered, the victim still needs to deal with a series of barriers to defend themselves. This is in agreement with studies that reported how victims of domestic violence felt that social support was weakened during confinement measures, especially in the first 6 wk, associated with lower trust in social and health services[130,131].

The rise in domestic violence and other stressors generated during the pandemic, contribute to aggravating the victims' lack of mental health, bringing physical and psychological consequences to the female population throughout their lives. In this way, the health impact can be translated through higher levels of stress, anxiety, depression, post-traumatic stress symptoms, and chronic environmental stress[132]. A study in the United Kingdom proved this by stating that women and people living with young children experience greater mental distress during the pandemic[133]. In addition, other studies around the world also confirmed that, in relation to men, women were at greater risk of acquiring mental health problems in this period[134-136].

CONCLUSION

In conclusion, the complex interaction between the biological and the social inequalities continually assists the development of the infection. The social inequalities contribute to the illness process, increasing the risk of contamination and morbimortality of the disease. On the other hand, the pandemic context favored the increase of the gaps and structural barriers pre-existing against the more vulnerable groups, leading to distress, social change in daily life, and greater illness of this population. Therefore, understanding the nuances that permeate the infection can assist both in the evaluation of the disease impacts and formulation of targeted measures able to encompass the individual necessities of the population, potentiating the prevention and recovery process of the health.

FOOTNOTES

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MINIREVIEWS

COVID-19 neuropsychiatric repercussions: Current evidence on the subject

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Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has affected the entire world, causing the coronavirus disease 2019 (COVID-19) pandemic since it was first discovered in Wuhan, China in December 2019. Among the clinical presentation of the disease, in addition to fever, fatigue, cough, dyspnea, diarrhea, nausea, vomiting, and abdominal pain, infected patients may also experience neurological and psychiatric repercussions during the course of the disease and as a post-COVID-19 sequelae. Thus, headache, dizziness, olfactory and gustatory dysfunction, cerebrovascular disorders, neuromuscular abnormalities, anxiety, depression, and post-traumatic stress disorder can occur both from the infection itself and from social distancing and quarantine. According to current evidence about this infection, the virus has the ability to infect the central nervous system (CNS) *via* angiotensin-converting enzyme 2 (ACE2) receptors on host cells. Several studies have shown the presence of ACE2 in nerve cells and nasal mucosa, as well as transmembrane serine protease 2, key points for interaction with the viral Spike glycoprotein and entry into the CNS, being olfactory tract and blood-brain barrier, through hematogenous dissemination, potential pathways. Thus, the presence of SARS-CoV-2 in the CNS supports the development of neuropsychiatric symptoms. The management of these manifestations seems more complex, given that the dense parenchyma and impermeability of brain tissue, despite protecting the brain from the infectious process, may

hinder virus elimination. Still, some alternatives used in non-COVID-19 situations may lead to worse prognosis of acute respiratory syndrome, requiring caution. Therefore, the aim of this review is to bring more current points related to this infection in the CNS, as well as the repercussions of the isolation involved by the pandemic and to present perspectives on interventions in this scenario.

Key Words: SARS-CoV-2; COVID-19; Central nervous system; Quarantine; Neurologic disorders; Mental disorders

Core Tip: Severe acute respiratory syndrome coronavirus 2 infection may also involve neurological and psychiatric manifestations, both by the viral action itself and by social distancing and quarantine. Headache, dizziness, cerebrovascular disorders, olfactory and gustatory dysfunction, neuromuscular abnormalities, anxiety, depression, and post-traumatic stress disorder may occur in this setting. Supporting these repercussions, this virus is able to reach the central nervous system by the interaction between the angiotensin-converting enzyme 2 and the transmembrane protease serine 2 expressed in the host nerve cells, and the viral spike glycoprotein. Finally, the management of these patients is complex and we review current evidence on the subject.

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INTRODUCTION

The coronavirus disease 2019 (COVID-19) outbreak has affected the whole world, causing fear and concern due to its transmissibility and severe life-threatening conditions. This pandemic infectious disease was first discovered in Wuhan, China, in December 2019[1]. Since then, the number of cases has increased, spreading rapidly globally and becoming a major pandemic disease[2]. By February 1, 2022, the World Health Organization confirmed more than 370 million cases worldwide, leading to 5658702 deaths[3].

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a β-coronavirus with positive spherical single-stranded RNA and spike proteins that project on the surface of the virion, which is characterized by its crown-shaped morphology[4]. Common symptoms are fever, fatigue, cough, dyspnea, diarrhea, chest tightness, nausea, vomiting, sputum production, anorexia, pharyngalgia, hemoptysis, and abdominal pain[5]. Frequently, SARS-CoV-2 contamination is associated with the nasopharyngeal and pulmonary tracts. However, important findings show that manifestations of this virus can be found in the central nervous system (CNS).

Neurological alterations have been described in patients with COVID-19, which vary from mild to fatal effects and can occur in severe or asymptomatic infection[6]. On the other hand, the global effects of SARS-CoV-2 infection result in various viral-related physical and mental health problems[7]. Thus, physical and social isolation, financial stress, and fear of contagion contribute to this scenario[8]. Therefore, this infection can present neuropsychiatric repercussions, such as headache, dizziness, anosmia, ageusia, neuromuscular dysfunction, anxiety, and depression[9], shown in Figure 1, in addition to other symptoms related to physiological and psychiatric changes, such as post-traumatic stress disorder (PTSD) and neuropsychiatric syndromes[8]. These manifestations seem to be caused as much by the infection itself as by social distancing and quarantine, which means that specific therapy should be used according to each case, seeking the most efficient healing process.

Therefore, this review describes the reported CNS manifestations associated with COVID-19, in order to help professionals who treat these patients, review the manner in which the virus reaches the CNS, and the intervention possibilities available to date in the literature.

METHODOLOGY

For this minireview, the authors surveyed relevant and current articles published in the United States

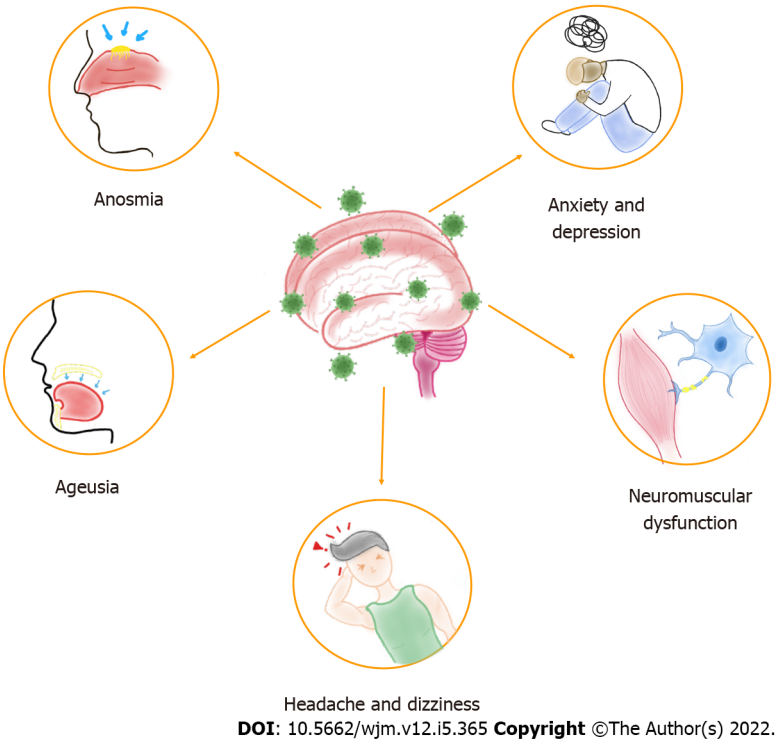

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Figure 1 Main neuropsychiatric repercussions of the severe acute respiratory syndrome coronavirus 2 infection, quarantine, and social distancing.

National Library of Medicine (PubMed). The descriptors used were COVID-19; SARS-CoV-2, coronavirus; angiotensin-converting enzyme 2 (ACE2), central nervous system, neuroimmune, cytokine storm, pathophysiology, neuroinvasion, neurological symptoms, neurological manifestations, olfactory dysfunction, gustatory dysfunction, ischemic stroke, hemorrhagic stroke, Guillain-Barré syndrome, neuropsychiatric symptoms, mental health, mental suffering, psychiatric disorder, and quarantine. The eligibility criteria were based on the discussion of aspects related to the neuropsychiatric repercussions of SARS-CoV-2 infection, dealing with everything from viral neuroinvasive mechanisms to neurological and psychiatric manifestations, due to the infection itself or to the need for full isolation in the read full-text. Thus, 26035 articles were found in the database, of which 109 complied with the inclusion criteria. The exclusion criteria were articles that did not address the topics in the title and/or abstract, or were written in languages other than English. The search was complemented by a manual search of the references of the included articles to identify additional references, 13 of which were added later, totaling 122 articles included in this review.

COVID-19 NEUROPSYCHIATRIC REPERCUSSIONS: CURRENT EVIDENCE

SARS-CoV-2 neuroinvasive mechanisms

One of the main mechanisms of neurological invasion of SARS-CoV-2 is through ACE2 receptors on host cells[6,10]. Several studies have shown the presence of ACE2 protein in human brain vessels, mainly in dopaminergic neurons, astrocytes, oligodendrocytes, and neurons[11-13]. ACE2 has also been observed in the substantia nigra, ventricles, middle temporal gyrus, posterior cingulate cortex, and olfactory bulb[11,13]. One study reported that ACE2 is more highly expressed in neuronal cell bodies than in axons and dendrites[14]. During infection, transmembrane protease serine 2 (TMPRSS2) activates the spike (S) glycoprotein on the SARS-CoV-2 envelope, which allows the virion to bind to ACE2 receptors[12,15]. TMPRSS2 is also found in oligodendrocytes and astrocytes located in the substantia nigra, cortex, and endothelial cells of cerebral capillaries[6,14], and is fundamental in the priming and activation of S proteins, which leads to membrane fusion. This interaction is responsible for SARS-CoV-2 entry on the CNS[14,16]. Later, the virus may affect the nervous system by disturbing the renin angiotensin system[11]. This process is exacerbated by slower circulation in the brain capillaries, which intensifies the interaction between the viral S glycoprotein with the ACE2 on brain cells[9,16]. Thus, CoV interacts with ACE2 expressed in the capillary endothelium, causing neuronal death and neurodegeneration[9,18].

Compared with SARS-CoV, SARS-CoV-2 has higher affinity to ACE2[15]. This enzyme is also known as a cardiocerebral vascular protection factor, and influences blood pressure regulation and anti-atherosclerosis mechanism, in view of its vasoconstrictor function and pro-inflammatory effects[9,19]. When the virus binds to the enzyme, it may cause elevated blood pressure and increase the risk of arterial wall rupture, cerebral hemorrhage, and ischemic stroke[13,17]. On other hand, ACE2 and TMPRSS2 have been detected in the nasal mucosa, one of the main mechanisms of entry into the brain[15,20]. Once the infection of the olfactory system occurs, the virus may be internalized in the nerve by endocytosis *via* the olfactory bulb and be transported retrogradely and disseminated to the brain *via* the cribriform plate[6,12,20].

SARS-CoV-2 may also affect the CNS indirectly, as the virus provokes alveolar and lung tissue damage[17,21]. This inflammation and edema caused by lung invasion disturbs oxygen exchange and results in hypoxemia. Thus, this scenario may lead to increased anaerobic metabolism in brain cells, brain hypoxia with vasodilation, hyperemia, ischemia, and brain edema and injury[17,20,21].

As previously mentioned, the virus can access the CNS through the olfactory nerve and also through the hematoretinal route. However, there is another potential pathway that allows CNS infection, which is *via* the blood-brain barrier (BBB), which occurs through hematogenous dissemination[22]. The BBB is one of the body's protections against disturbances in the nervous system. It is composed of endothelial cells, astrocytes, microglia and neurons, which act together. Under normal circumstances, these cells accurately regulate what enters and leaves the nervous system. However, in pro-inflammatory situations, such as that caused by SARS-CoV-2, this homeostasis is disturbed, which may be the genesis of virus entry into the CNS[23-25].

One factors that has been extensively studied currently is what causes this damage to the BBB, enabling infection in the CNS. The most likely one is the hyperinflammatory situation caused by the cytokine storm[1]. When viral replication occurs, damage-associated molecular patterns, which induce inflammatory states in neighboring cells through Toll-like receptors, are released. These receptors promote several cytokine production pathways. However, in COVID-19, there is hypercytokinemia. The main cytokines involved in this exacerbated process are tumor necrosis factor alpha (TNF-α), interferon gamma (IFN-γ), interleukin 2 (IL-2), IL-1RA, IL-2, IL-6, IL-7, IL-8, IL-9, and the granulocyte-macrophage colony-stimulating factor. These cytokines ultimately potentiate the activation of immune system cells, creating a cycle of increasing and perpetuating inflammation[26,27]. These processes are represented in Figure 2. Severe patients can also present with elevated levels of IL-17 compared to non-severe patients [28]. A comparative study showed a particularly strong inflammatory response triggered with the activation of this cytokine[29].

This cytokine storm damages the vascular endothelial cells of the CNS, affecting the integrity of tight junction proteins in the BBB, allowing the virus to enter. In addition to increased cytokines, the virus itself has cytopathic power, which can lead to pathogenic inflammation with cellular damage in the CNS including edema, ischemia, bleeding, and neurodegenerative disorders[1,30]. In pathological situations, the migration of cells from the immune system to the CNS is increased and in severe SARS-CoV-2 infection, it is even greater. This is supplanted in histopathological examinations of the brain parenchyma where large numbers of macrophages and lymphocytes were found[27].

Another factor that corroborates this increase in cell migration is that in the presence of damage to endothelial cells, the number of intercellular adhesion molecules increases. This favors the entry of the virus into the CNS, which is transported by cells of the immune system through a mechanism known as the "trojan horse" in which the virus enters the nervous system inside the host cell[31,32].

NEUROLOGICAL REPERCUSSIONS

SARS-CoV-2 infection can reach the CNS through the olfactory tract and access the cortex, basal ganglia and midbrain, which may be affected during propagation[33], supporting the existence of neurological symptoms as headache, anosmia, dysgeusia, dizziness, and impaired consciousness[34,35].

Headache and dizziness

Although this symptom is very nonspecific, several studies have reported the prevalence of headache in patients infected with SARS-CoV-2. The symptom may be present at the beginning of the disease, or even be the initial presentation of the clinical picture, as it may also be present after resolution of the infection[9]. In addition, this symptom may be related to other diseases present in the patient, and therefore, the prevalence varies greatly according to the work[36]. One study[28] indicated a combined prevalence of headache in about 8% of patients, whereas others reported higher numbers such as 20% [37] and 25%[38], as well as variation from 0.6% to 70.3%[39,40]. Accordingly, among the neurological effects reported in COVID-19 infection, especially headache, may be the result of complications of the viral infection, the host immune response, the presence of severe installed disease or even the drug therapy used[41].

The prevalence of dizziness is estimated to be about 8%[42] to 9%[5], which indicates a combined overall prevalence of 8.77% in a systematic review that analyzed neurological symptoms in patients

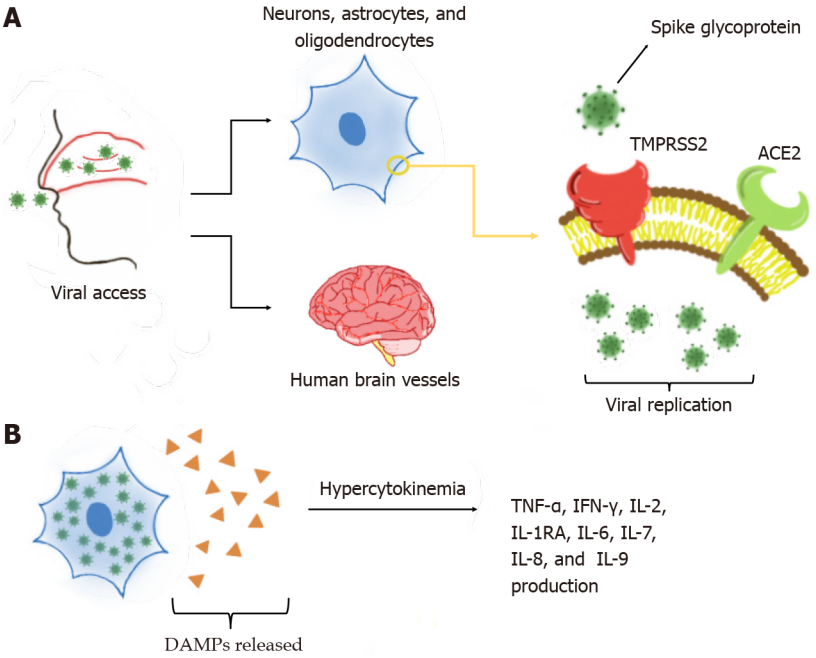

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Figure 2 Main neuroinvasive mechanisms of the severe acute respiratory syndrome coronavirus 2. A: Viral entry by olfactory epithelium and bringing between spike glycoprotein and angiotensin converting enzyme-2/transmembrane protease serine 2 expressed in the nasal mucosa; B: Cytokine storm induced by the damage-associated molecular patterns release. ACE2: Angiotensin converting enzyme-2; TMPRSS2: Transmembrane protease serine 2; DAMPS: Damage-associated molecular patterns; TNF-α: Tumor necrosis factor alpha; IFN-γ: Interferon gamma; IL: Interleukin.

infected with SARS-CoV-2[43]. As with headache, studies vary in determining the period in which dizziness appears in the clinical picture. However, a retrospective and observational case series reports dizziness as the main neurological symptom[44]. This is not a surprise, after all, since dizziness is historically reported in patients with viral infections. This symptom has been proposed to result from the neuroinvasive potential of the virus, such as direct injury by binding to the ACE2, or even by hypoxia and coagulation disorders[45]. Because it is nonspecific, it is important that the healthcare team perform a thorough investigation to determine its cause, given that it can be due to acute labyrinthitis, acute otitis media, vestibular neuritis, or even stroke due to COVID-19[46,47].

Disturbances of consciousness

In retrospective studies that analyzed the incidence of neurological symptoms in patients with COVID-19, a range of 3.3% to 19.6% was reported for disturbances of consciousness/delusion[48,49]. The cause of this involvement is still poorly understood, and may even be related to the post-inflammation inflammatory state, meningoencephalitis and encephalopathy, or may just be a sequela after a traumatic event [48]. Thus, a long-term follow-up is necessary for these patients, so that the real cause of this condition can be investigated with a detailed clinical history and serial imaging examinations.

Acute cerebrovascular disease

Viral neuroinvasion and subsequent central neuronal injury have been proposed to contribute to the pathogenesis of the disease. The interaction of SARS-CoV-2 with ACE2 receptors may be related to the episodes of intracerebral hemorrhage found in some cases, resulting in receptor inactivation and consequent dysfunction in blood pressure regulation[50]. In patients who already have pre-existing vascular risk factors, ischemic stroke is related to late complications in the severity of COVID-19 infection. The elderly with alterations in vascular hemodynamics resulting from age or associated pathology, once again, are groups that deserve special attention for the involvement of these injuries[51-54].

Studies have observed that patients presented neurological symptoms on average 3 to 4 d after the onset of respiratory symptoms, with hemifacial paresis, dysarthria, hemiparesis, loss of level of consciousness, hemiparesthesia and ataxia being symptoms found less frequently[51,52,55,56]. One study reported that the sex-based distribution of patients affected by COVID-19 shows that female patients report more central nervous system-related symptoms than males. This sex-based difference may be attributed to humoral and innate immune responses to viral infections that are more pronounced in women than in men[54-57]. Yet, autopsy results from COVID-19 patients showed that brain tissue was hyperemic and swollen and that some neurons degenerate[55,58].

Olfactory and gustatory dysfunction

Although they are now among the most well-known symptoms during SARS-CoV-2 infection, olfactory dysfunctions (OD), mainly hyposmia and anosmia, were initially seen as less relevant conditions in the pandemic context. Thus, OD throughout the pandemic became part of the symptoms that carry a warning sign of a possible ongoing infection, even when they appear in isolation[59].

Hyposmia, reduced sense of smell, and anosmia, the complete loss of smell, are common in patients with COVID-19. The OD can be evidenced subjectively, when the patient reports any degree of alteration, or objectively, when specific tests are applied in order to evidence the conditions of each individual. These parameters have guided researchers worldwide to carry out studies in which OD was evaluated in patients with COVID-19. In this context, a meta-analysis involving 3563 patients found that 47% of individuals had a self-reported loss of smell. In addition, researchers show that OD is more frequent in women and young patients. However, despite the relationship with the infectious condition, studies suggest that OD is not related to the severity of the condition[59,60].

The mechanisms that can cause OD have not yet been fully defined. In this context, studies point to several possibilities that can lead to olfactory impairment, such as conductive loss due to edema in the olfactory cleft, injury to the respiratory epithelium - due to the local inflammatory response with an increase in pro-inflammatory cytokines and chemokines such as IL-6 and IFN-γ, or lesion in the olfactory bulb, with neuronal damage. Symptoms begin on average within the 1st week of infection, vary in duration, and can last for weeks or months[61,62].

The impairment of smell has a direct impact on the quality of life of the individual, since it can make it difficult to recognize odors in food that indicate its disposal and odors associated with risks, such as flammable or toxic substances, for example. In addition, it can cause impairment in social interactions, and several studies associate olfactory dysfunction with a higher risk of developing depressive disorders[63].

Gustatory dysfunction (GD), mainly hypogeusia and ageusia, are prevalent symptoms in infected individuals. They are mostly associated with OD, but they may manifest in isolation in some cases, as pointed out by a systematic review that revealed a combined prevalence of GD of 43.93% in SARS-CoV-2-positive individuals[64]. Like OD, GD is more prevalent in young and female patients[65]. Furthermore, similarly to OD, the causes of DG are still uncertain. There are several hypotheses mainly involving the ACE2 receptors present on the tongue, which, being fundamental for the virus, may cause local inflammatory reactions, compromising taste functions. In addition, taking into account the potential for damage to the nervous system, there are hypotheses that relate DG to dysfunction of cranial nerves VII, IX, and X[66].

The gustatory function is able to identify sweet, salty, sour, bitter, and umami flavors. Among patients infected by SARS-CoV-2 with DG, sweet and sour tastes had the most altered sensitivity[65]. Among the DG, hypogeusia, mild to moderate, is more common than ageusia. For example, an Italian study with 72 participants found that hypogeusia occurred in 47.1% of cases, while ageusia occurred in only 1.4% of patients[67]. Like OD, GD is a common manifestation mainly in the 1st week of symptoms and has a resolution in a variable period with most patients completely regressing in approximately 10 d[68].

Guillain-Barré syndrome

Guillain-Barré syndrome (GBS) is considered a post-infectious and immune-mediated syndrome characterized mainly by manifestations such as rapid, progressive, and symmetrical limb weakness, impairment of tendon reflexes, which may be reduced or absent and to sensory impairment. Their subtypes are acute inflammatory demyelinating polyradiculoneuropathy (AIDP), acute motor axonal neuropathy, and acute motor and sensory axonal neuropathy, in addition to Miller Fisher syndrome, a variant. It is usually associated with respiratory or gastrointestinal infections caused by *Campylobacter jejuni*, the most common agent, *Mycoplasma pneumoniae, Haemophilus influenzae,* Epstein-Barr virus, influenza A, and *Zika virus*, for example[69-71].

However, during the COVID-19 pandemic, an increase in the number of GBS cases associated with individuals infected with SARS-CoV-2 was observed. In this context, a study conducted suggested an up to 2.6-fold increase in the baseline GBS case rate, from 0.93/100000/year to 2.43/100000/year. Furthermore, the authors noted that GBS associated with COVID-19 is more severe than those not associated with this virus[69]. In this sense, among patients positive for SARS-CoV-2, GBS is more prevalent in males and those aged over 60 years and, among the GBS subtypes, the most prevalent is AIDP[71-73].

As with other conditions arising from SARS-CoV-2 infection, the onset of GBS-related symptoms is variable, but studies suggest that the onset of symptoms occurs approximately during the 2nd week of infection, reinforcing the hypotheses of a post-infectious etiology of GBS. The causal mechanisms are still uncertain. However, there are hypotheses that relate the development of GBS to the cytokine storm that occurs during the second phase of infection, which usually occurs in the 2nd week of infection, related to the elevation of cytokines such as TNF-α, IL-1β, -6, -17 and IFN-γ, which are capable of causing tissue damage. In addition, there are hypotheses that relate GBS to autoimmune mechanisms by cross-reaction against ganglioside components of peripheral nerves, causing impairment of nerve

structures and, consequently, the development of the syndrome[72,74,75].

A summary of the hypotheses and mechanisms related to development of the neurological manifestations of the SARS-CoV-2 infection, as well as prevalence/incidence of these repercussions, are shown in Table 1.

Manifestations after infection

Neurological complications following COVID-19 infection are still poorly understood due to the recent onset of the pandemic and the question remains whether neurological symptoms are a definite sequelae or just a late effect of the disease. As the virus attacks and grows in lung tissue, alveolar gas exchange is disrupted due to systemic inflammation and edema, which can cause hypoxia and acid accumulation. A study describing the autopsy of 8 confirmed cases with SARS-CoV-2 infection reported brain swelling and severe neuronal damage[78], as did another study, with 18 brain autopsies of patients testing positive for the viral infection, indicated alteration by hypoxia in the cerebellum and brain, with loss of neurons in the cerebral cortex and hippocampus[79]. In addition, recent studies have shown that the infection caused by SARS-CoV-2 affects the central nervous system and the peripheral nervous system, and also directly or indirectly damages neurons, which causes long-term neurological sequelae[80].

PSYCHIATRIC REPERCUSSIONS

Along with the physical damages caused by SARS-CoV-2 infection, quarantine and social distancing significantly impacted the mental health of the population. In this sense, studies have demonstrated that during this period there was an increase in the rates of psychiatric manifestations such as irritability, stress, insomnia and depression[81], which can influence the individual's daily life even after the epidemic has ended.

Depression and anxiety

The subjectivity of life demonstrates an impact in reference to the development of mental disorders which contributes to different mental suffering rates for each group of people[82]. The necessity of staying at home for long periods[83], the vulnerability of the risk groups, increase in unemployment rates and publicity of false information contribute to both the illness of the population and increased number of suicides cases[84]. Other factors such as living alone, having children, being a student or a health worker, poor sleep quality, family support lack, less contact with friends and previous psychiatric history or substance abuse were also associated with the emergence of depression and anxiety[85].

A study conducted with the Chinese population showed that of the 1.210 respondents, about 30% had severe to moderate anxiety symptoms and 17% had severe to moderate depression[83]. Similarly, an online cross-sectional study conducted in China included 1.456 participants and assessed factors that influenced the mental health of adults during the pandemic. Its results showed that loneliness, depression and anxiety were associated with more somatic symptoms and lower self-efficacy. In addition, depression was associated with fear of infection, excessive alcohol consumption, and longer screen time. Loneliness was associated with single, divorced or widowed marital status, low education, medication use and frequent going out[86]. Furthermore, a survey of the Belgian population aged 18 years to 65 years reported that in just 2 wk of isolation the stress of individuals increased by about 25% [87].

PTSD

Literature reports also describe an increase in rates of PTSD in children, parents and even health care professionals after contact with infection, which demonstrates that subjective experience is also related to mental illness[88]. PTSD manifestations were related to higher perceived risk of infection, fear of infection, and self-assessment of higher negative influence due to the epidemic[86]. Corroborating, an electronic records cohort of 69 million individuals, of which 62.354 tested positive for infection, found that patients with COVID-19 had a higher incidence of unprecedented psychiatric diagnoses between 14-90 d after infection compared to other illnesses such as respiratory tract infections, skin infection, large bone fracture, urolithiasis, and cholelithiasis. Interestingly, previous psychiatric diagnoses also appear to be an independent risk factor for COVID-19[89].

Susceptibility to mental distress

The unpredictability of the outcomes of a possible infection can also increase susceptibility to mental distress, especially in people considered to be in the risk groups, which shows that subjective experience is an important predictor of the onset of psychological problems[90]. Studies performed during the pandemic reported a higher prevalence of mental disorders, such as anxiety in people with comorbidities or depression in individuals diagnosed with type 2 diabetes mellitus, when compared to the general population[91]. Similarly, minority groups such as immigrants, individuals with low access to health care and low socioeconomic status are more prone to mental disorders, since not only does the

Table 1 Main hypotheses, mechanisms related to development of the neurological manifestations of coronavirus disease 2019 and prevalence/incidence of these repercussions

Neurological repercussion	Hypotheses/mechanisms related to their development	Prevalence/incidence of manifestation
Headache	Complications of the viral infection, the host immune response, the presence of severe installed disease or even the drug therapy used[41,45]	The headache prevalence varies from 8%[56] to 25%[38] and 70.3%[40], according to the study
Dizziness	The direct injury by binding to the ACE2, or even by hypoxia and coagulation disorders may be related[45]	For dizziness, the prevalence is estimated to be around 8%[42] to 9%[5]
OD	Conductive loss due to edema in the olfactory cleft, injury to the respiratory epithelium or lesion in the olfactory bulb[61,62]	About 47% of individuals had a self-reported loss of smell. More frequent in women and young patients[59, 60]
GD	Local inflammatory reactions and the relationship with cranial nerves VII, IX, and X[66]	About 43.93% of the patients[64]. More prevalent in young and female patients[65]
Disturbances of consciousness	Post-inflammatory state, meningoencephalitis, or may just be a sequela after a traumatic event[48]	A range of 3.3% to 19.6% in COVID-19 patients[48,49]
Acute cerebrovascular disease	Intracerebral hemorrhage can be caused by viral interaction with ACE2 receptors and ischemic stroke is related to late complications in the disease severity[50]	The incidence of ischemic stroke in patients with COVID-19 was reported to be between 0.9%[76] and 4.6%[77]
GBS	There are hypotheses that relate the development of GBS to the cytokine storm and autoimmune mechanisms by cross-reaction[74,75]	A study suggested an up to 2.6-fold increase in the baseline GBS case rate, from 0.93/100000/yr to 2.43/100000/yr

ACE2: Angiotensin-converting enzyme 2; COVID-19: Coronavirus disease 2019; GBS: Guillain-Barré syndrome; GD: Gustatory dysfunction; OD: Olfactory dysfunction.

pandemic contribute to increasing marginalization and discrimination of these groups, but they are also considered more susceptible to infection and deaths caused by COVID-19[92]. In addition, women were also more affected than men by major depressive disorders and anxiety[93]. Violation of women's human rights with increasing rates of domestic violence and restrictions on access to prenatal health care services also contribute to greater mental illness in this group[94].

On the other hand, a preexisting mental health condition may be aggravated by the pandemic, as people diagnosed with mental disorders are considered more vulnerable to changes in their health status due to varying risk factors[95]. Interestingly, Pan *et al*[96] noted that people who did not have a psychiatric diagnosis of anxiety, depression, or obsessive-compulsive disorder prior to the pandemic reported an increase in symptoms related to these comorbidities. However, those individuals who already had a diagnosis of one of these disorders did not experience greater worsening of symptoms post-pandemic.

Mental health of the healthcare professionals

Healthcare professionals who worked on the front lines in the pandemic are a particularly affected population at higher risk of developing psychological distress and mental health impairment[97]. In this context, a cross-sectional study of 3852 healthcare professionals assessed the mental health of professionals who worked in the COVID-19 pandemic and SARS outbreak. The authors reported that health care workers achieved moderate and severe scores for symptoms of PTSD, anxiety, and depression[98]. A summary of highlights related to development of the psychiatric disorders in COVID-19 are shown in Figure 3.

INTERVENTIONS

The management of SARS-CoV-2 infection seems more complex when it involves the CNS. The dense parenchyma and impermeability of brain tissue, despite protecting the brain from the infectious process, may also hinder virus elimination. Still, the treatment of patients with neurological complications from this infection requires caution, because some drugs used in non-COVID-19 situations can lead to worsening of the disease-related acute respiratory syndrome, such as corticosteroids and immunosuppressant[99,100]. Moreover, viral damage can affect renal, immunological, hematological, hepatic, pulmonary and cardiac organ systems, as well as lead to pharmacokinetic changes that influence the absorption, distribution, metabolism and/or excretion of medications, such as psychotropic drugs. Susceptibility to side effects may be increased and adjustments in treatment regimens should potentially be considered[101], in addition to the pro-inflammatory, pro-thrombotic and arrhythmogenic implications of this infection[102]. Therefore, the approach to COVID-19-positive patients with neuropsy-

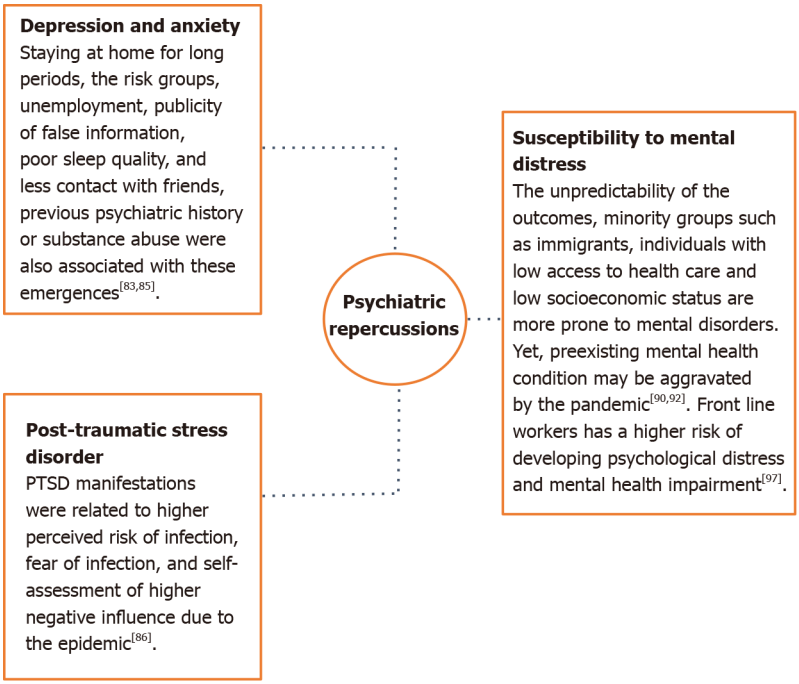

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Figure 3 Highlights related to development of the psychiatric disorders in coronavirus disease 2019. PTSD: Post-traumatic stress disorder.

chiatric repercussions still needs further long-term studies for evaluation and establishment of guidelines.

Neurological repercussions

One study reports the requirement for appropriate neuroimaging protocols in coronavirus infections to detect encephalitis, leptomeningeal and vascular changes such as stroke, microhemorrhages and cerebral infarction[103]. It is important that appropriate therapies are applied at the correct time, and that assessment of adjacent comorbidities, as well as damage to other organs and general condition is done using the sequential organ failure assessment score, which influences the COVID-19 prognosis [104,105]. Severe individuals can present right levels of the inflammatory markers, as C-reactive protein and D-dimer, and administration of tissue plasminogen activator in these patients with ischemic stroke predicted worse prognostic[44,106]. Thrombectomy can be used, evaluating the risks and benefits of therapy, and antiplatelet and anticoagulant agents remain uncertain. Thus, due to the lack of definitive studies, it is recommended to follow the existing guidelines[104].

Patients with demyelinating conditions and mild infection may be acceptable to continue treatment and the interruption may be considered in the use of potent immunosuppressant with risk factors for severe disease, returning after 4 wk or complete remission of symptoms[107]. The remission time of olfactory and gustatory dysfunction is controversial in literature, with studies reporting spontaneous resolution in 1 to 3 wk[108]. On the other hand, the smell performance of SARS-CoV-2-positive patients with mild or no symptoms can also not recover completely after 4 mo or more of acute infection[109]. Therefore, this treatment is still uncertain, but studies point to benefits of practicing olfactory training for those with persistent symptoms. In addition, some studies evaluate the role of local corticosteroids in recovery, but there is no consensus[110]. A study evaluating the efficacy of locally applied steroids in the form of fluticasone nasal sprays for olfaction disorders and triamcinolone paste for taste disorders reported that olfaction and taste function improved significantly in patients with COVID-19 within 1 wk [111]. Treatment for GDs is rarely addressed in the currently published literature, so more studies are needed to understand the best therapeutic options, especially in cases in which symptom regression does not occur as expected. Yet, there are different treatments that can be used against GBS, depending on the health structure and clinical context of each individual. Thus, among treatment possibilities, the use of intravenous immunoglobulins, plasmapheresis, or corticosteroids, alone or in combination, may be necessary[73,112].

The management of headache during SARS-CoV-2 infection can be accomplished by administering previously established therapeutic regimens for the treatment of acute crisis[113]. Non-steroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen, are already widely used drugs in the treatment of headache crises and, although they are demonstrated during infection, their use is questioned. Reports in the literature note that NSAIDs could be related to increased ACE2 levels[114], which would contribute to ease the entry of the virus into the host cell as more viral receptors would be expressed,

and negatively impact the immune system through cyclooxygenase inhibition, decreasing neutrophil chemotaxis and leading to an inefficient response against the virus, and reducing the expression of lipoxins and resolving that contribute to the resolution of inflammation. However, there are not enough studies to prove or rule out these theories[115]. On other hand, the administration of triptans like sumatriptan has been shown to be quite effective in the treatment of migraine, but despite this, for the drug choice, it is also important to consider both the patient's pre-existing comorbidities and the severity of the infection at the time[116]. Other therapies such as the administration of paracetamol, which is considered a safe and effective drug in these cases[114], neuroleptics such as chlorpromazine and neuromodulation devices can also be considered for treatment[113,117]. Lastly, the use of oral corticosteroids has also been related to improving migraine cases and managing the transition to cluster headache; however, studies have reported that these drugs could also contribute to perpetuating the replication of the virus[117].

Psychiatric repercussions

With regard to psychiatric manifestations secondary to SARS-CoV-2 infection, delirium is mainly related to the hyperactive/mixed variety associated with elevated anxiety, and isolation itself is considered a factor that can both trigger and/or increase delirium symptoms[118,119]. This makes management difficult and lower potency antipsychotics such as olanzapine and quetiapine are preferred[118] and haloperidol is the most considered for agitation control in delusional patients[101]. Immune modulation therapies for depression secondary to infection-initiated hyperinflammation are being investigated, such as IL-6 inhibitors and melatonin[120], but more studies are required. On the other hand, technologies with online psychotherapies can support the pediatric population in this situation[121], cognitive behavioral therapy and mindfulness-based cognitive therapy can also assist in stress reduction[122].

Although low dosages of benzodiazepines are indicated in anxiety, these drugs have the potential for respiratory depression and the risk and benefits in patients with respiratory symptoms should be considered. Thus, according to the situation, gabapentin, hydroxyzine or lower doses of selective serotonin reuptake inhibitors (SSRIs) can be used, as well as non-pharmacological interventions, such as psychotherapy[101]. Treatment of PTSD typically involves SSRIs and serotonin-norepinephrine reuptake inhibitors, and the potential risks should be analyzed on a case-by-case basis. Paroxetine is not recommended due to the short half-life, anticholinergic side effect profile, and increased risk of drug interactions[102].

CONCLUSION

Thus, in this review we described the SARS-CoV-2 ability to infect the CNS and to cause manifestations related to neurology and psychiatry. Some nonspecific symptoms, such as headache, may be part of the initial clinical presentation as also be present after the resolution of the infection. Viral interaction with ACE2 receptors may be related to the onset or worsening of episodes of cerebrovascular disorders and demyelinating conditions, and to the development of olfactory and taste dysfunction by migration through the olfactory tract, one of the virus pathways. Yet, mental illnesses such as depression, anxiety, and PTSD may be caused by the social distancing and quarantine in both patients and health care workers who worked on the front lines, and these disorders may remain even after the pandemic has ended. Our work contributes to the elucidation of the disease pathogenesis, as well as the understanding of clinical presentation, since not all patients will present with a classic respiratory condition. Finally, the pandemic effects still need to be evaluated in the long term and more studies are necessary to clarify guidelines and establish the adequate management of these individuals.

FOOTNOTES

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MINIREVIEWS

Diagnosis and management of small bowel neuroendocrine tumors: A state-of-the-art

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Abstract

This review provides an update on the epidemiology, pathophysiology, symptoms, diagnosis and treatment of neuroendocrine neoplasms (NENs) of the small bowel (SB). These NENs are defined as a group of neoplasms deriving from neuroendocrine cells. NENs are currently the most common primary tumors of the SB, mainly involving the ileum, making the SB the most frequently affected part of the gastrointestinal tract. SB NENs by definition are located between the ligament of Treitz and the ileocecal valve. They are characterized by small size and induce an extensive fibrotic reaction in the small intestine including the

mesentery, resulting in narrowing or twisting of the intestine. Clinical manifestations of bowel functionality are related to the precise location of the primary tumor. The majority of them are non-functional NENs and generally asymptomatic; in an advanced stage, NENs present symptoms of mass effect by non-specific abdominal pain or carcinoid syndrome which appears in patients with liver metastasis (around 10%). The main manifestations of the carcinoid syndrome are facial flushing (94%), diarrhea (78%), abdominal cramps (50%), heart valve disease (50%), telangiectasia (25%), wheezing (15%) and edema (19%). Diagnosis is made by imaging or biochemical tests, and the order of request will depend on the initial diagnostic hypothesis, while confirmation will always be histological. All patients with a localized SB NEN with or without near metastasis in the mesentery are recommended for curative resection. Locoregional and distant spread may be susceptible to several therapeutic strategies, such as chemotherapy, somatostatin analogs and palliative resection.

Key Words: Neuroendocrine; Tumor; Small bowel; Small intestine; Gastrointestinal disease; Treatment; Survival

Core Tip: There are reviews in the literature regarding neuroendocrine tumors in the gastrointestinal tract specifically in the small bowel. Nevertheless, this is a first mini review to synthesize the latest data related to epidemiology, pathophysiology, clinical manifestations, diagnosis and treatment of small bowel neuroendocrine tumors.

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INTRODUCTION

Langhans was the first person to describe small bowel (SB) neuroendocrine neoplasms (NENs) in 1867, as a polypoid tumor of the small intestine[1]. Nowadays, NENs are described as a heterogeneous group of neoplasms derived from neuroendocrine cells. The term NENs encompasses well-differentiated NENs and poorly differentiated neuroendocrine carcinomas (NECs)[2]. NENs commonly arise from the gastrointestinal tract[3,4,40].

NENs can progress throughout the gastrointestinal tract, but are specifically seen in the small intestine (45%), rectum (20%), appendix (16%), colon (11%), pancreas (5%-10%) and stomach (7%)[5] (Figure 1).

NENs account for 1.0%-1.5% of all gastroenteropancreatic neoplasms[6]. SB NENs continue to increase in incidence and are today the most frequent primary malignancies of the SB[2]. This growing phenomenon seen since the 1970s is possibly due to the detection of early-stage disease[7,8].

The aim of this manuscript is to carry out not only an updated narrative review on the diagnosis and treatment but also to synthesize the data related to epidemiology, pathophysiology and clinical manifestation of SB neuroendocrine tumors.

MATERIALS AND METHODS

We conducted a bibliographic review using articles indexed in PubMed/Medline, Scopus, Embase and Scielo, published between 2000 and 2022. The Medical Subject Headings used were: "Neuroendocrine Tumors", and "Small Bowel" or "Small Intestine". The research was limited to human-related articles. The type of articles included were: Clinical trials, prospective cohort studies, retrospective and cross-sectional studies, as well as systematic reviews and meta-analyses.

The quality of our narrative review was assessed using the SANRA scale[9], which covered the following topics: Description of the literature search, statement of the review aims, referencing, explanation of the review's importance, presentation of relevant and appropriate endpoint data and scientific reasoning.

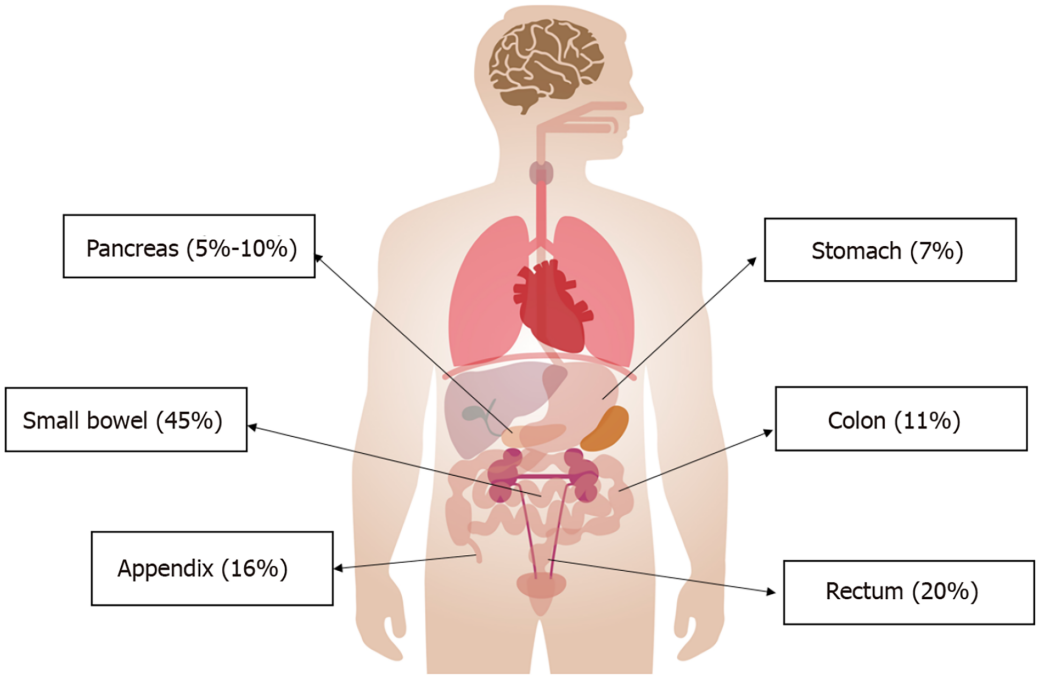

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Figure 1 Incidence of neuroendocrine tumors in the gastrointestinal tract.

EPIDEMIOLOGY

Small bowel cancers represent only 0.6% of all cancers and less than 5% of gastrointestinal (GI) cancers according to figures from the United States[10]. However, its incidence is increasing, reaching a growth of over a 100% in the last 40 years[10].

The two main types of SB neoplasms are adenocarcinoma of the small intestine, and NENs. Although in the 1980s, adenocarcinoma was predominant with 42%, in 2005 it had decreased to 33%, while NEN at the same time increased from 28% to 44%, positioning itself as the most frequent type of primary tumor[11]. Yao *et al*[6] also reported an increase in NENs of 6.4-fold from 1.31/100000 to 6.98/100000 over the timeline 1973 to 2016. In 2020, the incidence of NENs of the small intestine was estimated to be 1.2 cases per 100000 population in the United States[2].

It is thought that the rise in cases is the result of the development of better diagnostic methods, as often they are detected incidentally in endoscopic or imaging studies[11,12]. In addition, the increase in NENs compared to adenocarcinomas may be explained by the increased survival of patients with small intestine cancers, as NENs usually have a better prognosis[11].

Unlike adenocarcinomas, which are more frequent in the duodenum, small intestine NENs are more frequent in the ileum[11]. Some genetic mutations predispose to the development of NENs. The most common predisposing condition is multiple endocrine neoplasia type 1 and represents around 5 to 10% of these tumors[11].

Studies reporting the duration of symptoms preceding diagnosis varies widely, from a median of 4.3 mo up to 9.2 years[1]. Liver metastasis is seen in as many as 61%-91% at the time of diagnosis[11]. Among the risk factors associated with metastatic disease are the location in the jejunum or an unspecified site, the histology of neuroendocrine carcinoma and being a patient from a rural area[13].

The median overall survival (OS) of SB NENs is 14 years, while localized and well differentiated tumors showed a better survival. In multivariate analyses, factors that had a significant correlation were race, age, stage and site. In contrast to pancreas NENs, patients with bowel NENs are 1.5 times more likely to survive[11].

There is no objective way to define the prognosis of these patients; however, tools have been created such as the Modlin Score Nomogram that addresses 15 parameters whose objective is to determine the prognosis and guide treatment[14]. The use of this tool in tertiary referral hospitals made it possible to identify patients accurately with low and high risk of death, although Kelly and co-authors in their 2019 study indicated that it was not applicable to all patients[15].

The Epidemiology and End Results (SEER) database included 73782 patients diagnosed with NENs between 1973 and 2014 in a surveillance analysis. SB NENs were found to be the second tumor with the best prognosis, after rectum NENs[16]. Summing up the localized, regional and metastatic forms of the disease, despite the heterogeneity of these tumors, the decrease in mortality rates of all forms is well-known, regardless of an increasing incidence. In addition, although comparisons between studies is

difficult due to different patient classifications, cohorts and methodology, the observations in diagnostic and therapeutic advances made, are usually similar[13].

PATHOPHYSIOLOGY

Neuroendocrine cells release hormones by stimulation of the nervous system. They are found throughout the body, such as in the skin, lungs, gonads, pancreas, the GI tract, pituitary gland and adrenal glands. NENs are neoplasms that originate from these cells. Depending on their location, their clinical behavior is very heterogeneous[2] (Figure 2).

SB NENs are often small, multifocal, difficult to locate pre-surgically, and may not be found during surgical exploration[17]. They represent 30% of neoplasms found in the SB[18]. By definition, SB NENs are located between the ligament of Treitz and the ileocecal valve. Although duodenal NENs are sometimes included with jejunal and ileal NENs under the umbrella term "SB NEN", these tumors are clinically and biologically different and should not be considered as representatives of the same entity [1].

After the lung, the small intestine is the next most common location for NENs[1]. The risk factors that increase the incidence of SB NENs, have to be considered and include: A habit of smoking[19], a possible family history of cancer and the antecedent of gallbladder disease and cholecystectomy. All of them are associated with a 1.5-fold higher risk of developing SB NEN[20].

Mutation of the MutY human homologue (MYH) gene is associated with SB neuroendocrine tumors and is the main genetic background described in DNA base repair by excision[21-23] which fail in a hereditary form of SB NEN. Clinically, hereditary forms tend to be isolated endocrinopathies; however, further research is necessary.

SB NENs present in many forms, depending on the stage of the disease and the tumor burden at diagnosis. Approximately 30% of patients with SB NENs will have metastasis at the time of diagnosis, and another 40% will have regional lymph node involvement[5]. Primary tumors, in spite of being characteristically small, may cause an extensive fibrotic reaction in the SB and mesentery, resulting in narrowing or twisting of the intestine and potentiate mesenteric ischemia[1].

Metastasis of SB NENs is most commonly from the frequently seen primary site of both the small intestine as well as the pancreas. Some patients with SB NENs have synchronous or metachronous pancreatic NENs (PNENs), and it is frequently unclear whether these are separate primary tumors or metastasis. In a case series, in almost two-third of the evaluated patients, the pancreatic tumor was a metastasis of the SB NEN primary tumor, while in the remaining third of patients it represented a separate primary tumor. Determining the origin of these tumors can guide the choice of systemic therapy and surgical management[24].

CLINICAL MANIFESTATIONS

The clinical manifestations are caused by the location of the primary NEN and its functionality. Most of them are non-functional, which usually have no or very few symptoms in the early stages of the disease; late symptoms are due to its mass effect or liver metastasis[25-28].

In general, the most common symptom of intestinal NENs is nonspecific abdominal pain that leads to Computing Imaging studies. Intestinal NENs can present with GI bleeding and anemia. Occasionally, NENs grow large enough to obstruct the extrahepatic bile duct or GI tract, causing jaundice or intestinal obstruction, respectively. Rarely, an intra-abdominal mass is palpable on physical examination, prompting further diagnostic studies[26]. In addition, around 15%-20% of SB NENs are symptomless and are detected incidentally, which is more frequent in patients with localized disease[1].

In patients with metastatic disease, about 10% develop carcinoid syndrome (CS), with predominance in liver metastasis. Of the wide variety of manifestations, the main manifestations are: Facial flushing (94%), diarrhea (78%), abdominal cramps (50%), heart valve disease (50%), telangiectasia (25%), wheezing (15%) and edema (19%)[29]. Almost all SB NENs produce a wide variety of biologically active peptides, including serotonin, neurokinin A, and histamine, which are responsible for CS. However, for tumors limited to the SB and its regional lymph nodes, these components are inactivated by the liver and hormonal symptoms are rare[1].

With the development of distant metastasis, the hormones secreted by SB NENs are able to bypass the portal circulation, leading to the development of CS. This syndrome was first described by Thorson in 1954. Carcinoid symptoms may be spontaneous or caused by stress, exercise, or ingestion of ethanol and amine-rich food such as chocolate or cheese[5]. The flushing associated with CS is typically transient and affects the face, neck and the upper part of the trunk[1].

The cardiac manifestations of CS, called "carcinoid heart disease", primarily affect the right side of the heart, causing valvular fibrosis. Cardiac involvement is seen in at least 20% of patients. The cause is believed to be related to high levels of serotonin that induce a fibrotic reaction in the right heart. However, the incidence is declining, possibly due to the widespread use of somatostatin analogs (SSAs).

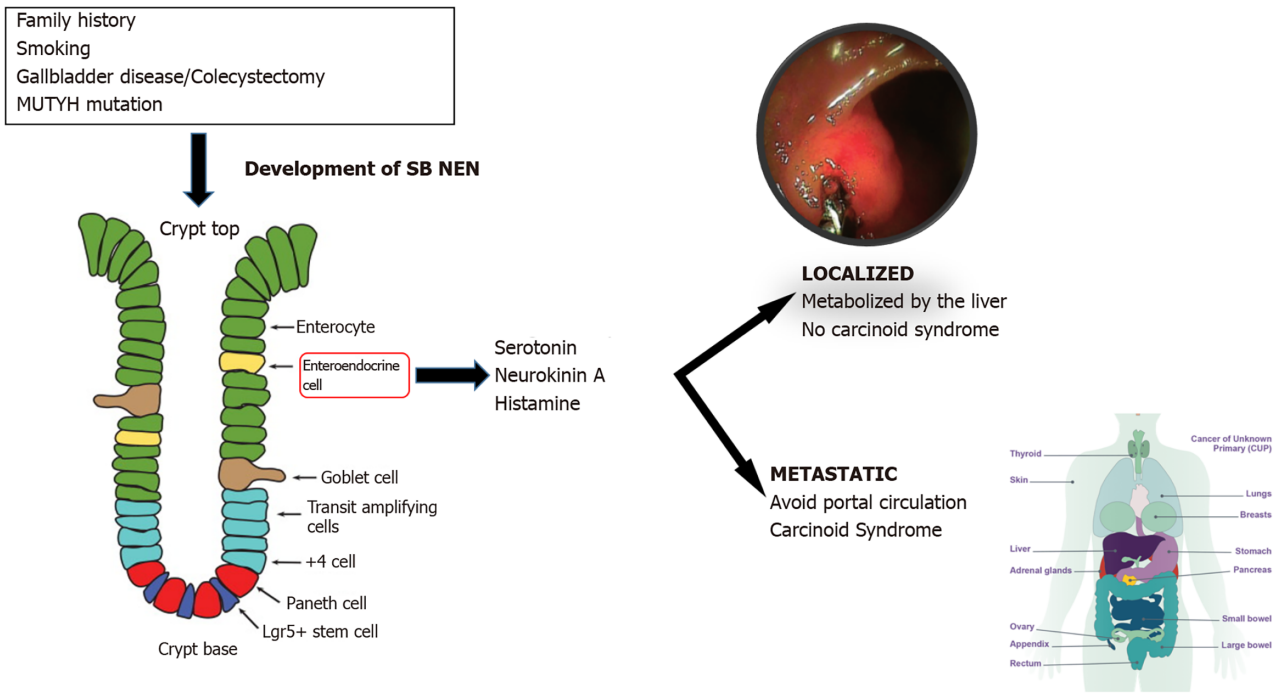

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Figure 2 Pathophysiology of small intestine neuroendocrine tumors. MUTYH: Human mutY homologue; NEN: Neuroendocrine neoplasms; SB: Small bowel.

The presence of carcinoid heart disease predicts a worse prognosis[1]. This variety in presentation, combined with the relative rarity of the tumors and the nonspecific nature of the symptoms, makes diagnosis of these tumors difficult. Although the median duration of symptoms before diagnosis is 4 to 5 mo, misdiagnosis is common and a delay in diagnosis of up to 10 years has been described in the literature[1].

Published series from tertiary referral centers, mention the proportion of patients with distant metastasis of around 60% to 80%. One possible explanation for this is perhaps because early-stage lesions are removed in emergency surgeries for intestinal obstructions in less complex hospitals, while the more advanced stage of the disease is referred to these larger hospitals[30,31].

DIAGNOSIS

For the diagnosis of NENs, there are currently various methods available. The initial methods can be both imaging and laboratory tests; the order in which they are requested will depend on the form of clinical presentation and the initial diagnostic hypothesis. Confirmation will be histological, requiring a biopsy by endoscopy. Octreotide scan, video capsule endoscopy (VCE) and double-balloon enteroscopy (DBE) are the auxiliary exam options for diagnosis. Series reports catalog them as having a diagnostic yield of 85%, 10% and 83%, respectively. In occult SB NENs, capsule endoscopy appears to be superior to enteroscopy but may underestimate tumor burden[17].

Biochemical testing

For most patients, biochemical testing and anatomic or functional imaging will have preceded definitive diagnosis of SB NEN made by an immunohistochemical study of the tumor[6]. In addition to the hormones and neuroamines responsible for CS such as 5-hydroxyindoleacetic acid (5-HIAA) in plasma or urine[32], SB NENs secrete chromogranin A (CgA), pancreastatin, and serotonin which can be used as biomarkers for diagnosis and surveillance[32]. CgA is an acidic glycoprotein secreted by NENs, and has been extensively studied. CgA is sensitive and specific for the diagnosis of NEN, correlates with disease burden, and can predict survival. Nevertheless, renal failure, severe hypertension, vitamin B12 deficiency and proton pump inhibitor therapy can cause false CgA elevations. Serial pancreastatin measurements are useful in predicting and monitoring response to therapy[33]. A 24-h urine sample monitoring 5-HIAA, indicates serotonin breakdown. This test is highly specific for the diagnosis of SB NEN, but patients should be advised to avoid various serotonin-rich foods during collection[2].

Biochemical tests are widely used both for the diagnosis of SB NEN and for monitoring the course of the disease, but there is no agreement on how often they should be measured or how their measurement

should influence treatment decisions[33].

Endoscopic, radiological and molecular investigations

The endoscopic technique of VCE and DBE are the most helpful exams in jejunal and ileal NENs. They allow location of the primary NEN in metastatic disease, where a basic study has been negative, to identify multifocal disease. This might change the management and prognosis. In addition, other studies have reported that multifocality does not seem to have an impact on survival or recurrence[18].

Those patients who present with hot flashes and diarrhea will probably undergo biochemical tests first, while those whose main symptom is abdominal pain or obstructive symptoms will require anatomical imaging such as computed tomography (CT) or may even be diagnosed only after an emergency surgical intervention[33].

For anatomical studies of SB NEN, CT, magnetic resonance imaging, and ultrasound are performed, while for functional studies positron emission tomography (PET) with Gallium and somatostatin receptor-based single photon emission computed tomography are carried out. Functional imaging using PET is essential for detecting small lymph node metastasis, tiny primary tumors in the SB, initial bone and bone marrow metastasis and more accurate assessment of occult liver metastasis[3]. Anatomical images provide the location of the tumors for surgical planning, while functional images have higher sensitivity and indicate the occult presence of metastasis or mistaken evidence of recurrence[2,33].

NENs of the SB are rarely visualized on CT. They are usually just millimeters in size. However, mesenteric lymph node metastasis might well appear as spiculated masses on contrast-enhanced CT, sometimes including calcifications and the regional presence of fibrosis due to its desmoplastic reaction. Additionally, as many as 30% can be multifocal[2]. CT angiography can provide details of valvular involvement. Despite this, morphological images generally significantly understate the disease[2].

Pathology

For tumor classification, the Ki67 index or the number of mitoses per 10 high power fields (HPF) is used. NENs are subclassified into NENs and NECs. Grade 1 NENs have < 2 mitoses per 10 HPF or a Ki67 of < 3%. Grade 2 NENs show a Ki67 index from 3 to 20%, or 2 - 20 mitoses per 10 HPF. Grade 3 NENs give a Ki67 index of > 20%, or > 20 mitoses per 10 HPF. Further classification into G3 NENs and G3 NECs is based on their differentiation. G3 NECs are poorly differentiated but Grade 3 NENs are well differentiated[2].

Figure 3 summarizes the initial approach sequence of the patient with a suspected SB NEN and which tests should be requested depending on the form of clinical presentation.

TREATMENT

Treatment of a SB NEN depends on the staging of the disease, and whether it is locoregional or metastatic (Figure 4).

Management strategies for SB NEN include not only possible treatment of all stage tumors or metastasis, and if present, carcinoid heart disease or tumor-related symptoms and syndromes[2].

The management of these lesions is complex due to the difficulty in diagnosis, hormone secretion and more frequently, its presentation as an advanced disease. Even patients with advanced disease can have a long survival time. There are different aspects that make it difficult to determine the optimal management[34].

All patients with localized SB NEN with or without regional mesentery metastasis should be considered for curative resection. Therefore, multimodal treatment is required[2]. Although surgery is curative in most cases, recurrence rates of 42% in liver NEN have been published[1,35].

In the surgical area, meticulous exploration of the abdomen with palpation of the SB is recommended intraoperatively; this is superior to reference imaging for the detection of SB NENs, as up to 70% of these tumors are overlooked by imaging. Additionally, between 30%-54% of SB NENs are multifocal and just millimeters in size, which are very difficult to see on imaging. Therefore, a laparoscopic study is not recommended[2]. The abdomen should also be carefully examined for evidence of liver and peritoneal metastasis, reported in 20% and 60% of cases, respectively, undergoing SB NENs surgery[1].

In SB NENs, total resection it is not necessary, only the primary tumor and selective resection of the mesenteric nodes is required, taking into account the preservation of bowel function. The length of bowel resected is independent of the number of lymph nodes removed. In up to two-thirds of patients, metastasis outside the "expected" lymph node region is found, and to prevent unresectable locoregional recurrence, an extensive lymphadenectomy is required[2]. A series of reports of surgeries for SB NENs where the resection included 12 or more nodes, was related to better OS outcomes, in patients without distant metastasis[2].

If the primary tumor is located in the terminal ileum, a right hemicolectomy with or without lymphadenectomy is indicated[36]. In cases with stage IV asymptomatic SB NEN, early locoregional surgery as a prophylactic measure is controversial, as there are no convincing data associated with favorable survival outcomes, compared with locoregional surgery later in its development. SB NEN can

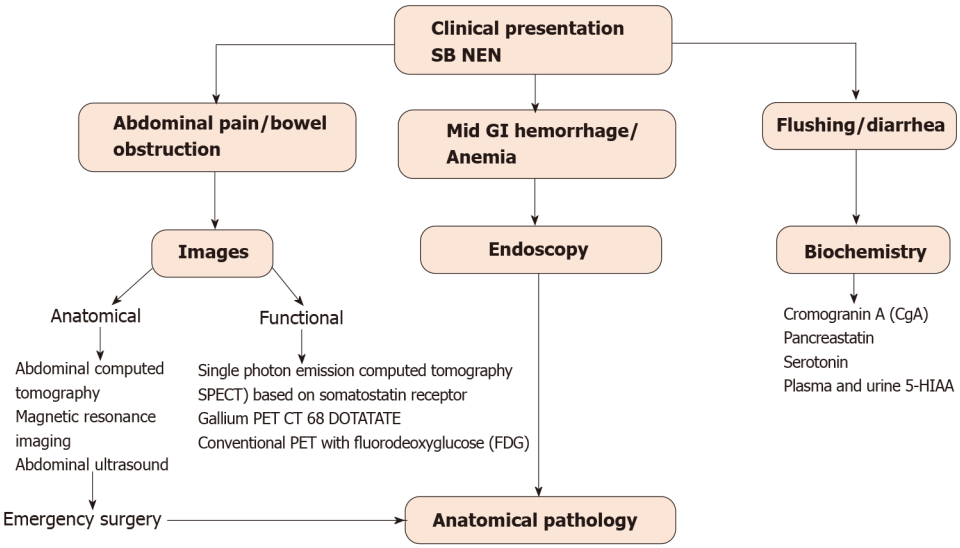

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Figure 3 Diagnostic algorithm for small intestine neuroendocrine tumors. GI: Gastrointestinal; NEN: Neuroendocrine neoplasms; SB: Small bowel; PET: Positron emission tomography.

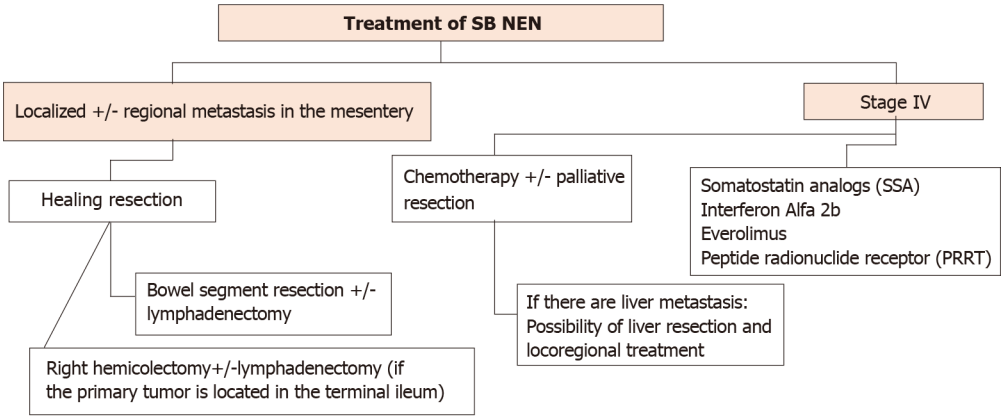

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Figure 4 Management of small intestine neuroendocrine tumors. NENs: Neuroendocrine neoplasms; SB: Small bowel.

be associated with peritoneal carcinomatosis (PC) in up to 30% of cases. As PC can cause fatal intestinal obstruction with a registered mortality of 40%, resection of peritoneal tumors should be part of the locoregional surgery[2].

Resection of the primary tumor in the setting of unresectable SB NEN liver metastasis may prevent ileus, intestinal obstruction, and desmoplastic reactions, and is registered in a retrospective study to prolong survival, independent of the tumor grade. However, such studies are biased toward an aggressive approach in patients with better baseline status, so it is unclear whether this intervention is beneficial versus the underlying characteristics of the cases[2].

Patients with metastatic NENs to the SB have a favorable prognosis, compared with other GI malignancies. An OS of 103 mo for cases with well-differentiated tumors was reported in some series between 2000 and 2012[6].

The first-line treatment of NENs consistes of SSAs, which is also the case in functional and non-functional metastatic NENs of the SB, to control CS symptoms and due to their antiproliferative effects [37,38]. The treatment consists of injections of octreotide LAR or lanreotide, which are long-acting SSAs, every four weeks. Short-acting octreotide injections are given in cases to improve symptomatic control or as a rescue therapy[1]. Octeotride LAR plus interferon alpha have shown beneficial effects by inhibiting hormone secretion and proliferation in NENs in the past decades[39].

Everolimus has been studied in advanced stages of NENs. It is a rapamycin inhibitor, used to treat CS (RADIANT-2 trial) and advanced non-functional NENs (RADIANT-4 trial). In the RADIANT-2 trial, better OS was observed after treatment with everolimus and octreotide LAR versus treatment with octreotide LAR only; however, the difference was not statistically significant[33]. Results from the

RADIANT-4 trial did show a statistically significant improvement in median progression-free survival when everolimus monotherapy was compared with a placebo (11.0 *vs* 3.9 mo). Based on these findings, everolimus is only approved for use in progressive non-functional NENs, but is often used in patients with progressive disease regardless of tumor functionality[1,38].

Since 1992, peptide receptor radionuclide therapy (PRRT) has been used for the treatment of NENs. In PRRT, radionuclides such as Yttrium-90 (90Y) and Lutetium-177 (177Lu) are directly delivered to the tumor by radiolabeled SSA8. In the 229 patient NETTER-1 trial, all patients had well-differentiated, metastatic NENs. It was found that the PRRT treatment group had a significantly better median OS and a better response rate compared with the placebo group (18% *vs* 3%)[1,40].

Cytotoxic chemotherapy is also used in the treatment of PNENs, and has been shown to have an inferior role in well-differentiated SB NENs[1]. Due to easy oral administration, and their low adverse effect profile, capecitabine and temozolomide remain good practice second- or third-line choices in patients with progressive SB NENs[1].

Small intestine NECs are extremely rare. Regardless of the primary site, cisplatin or carboplatin and etoposide are used as first-line treatment, and due to the poor prognosis of NEC, they are generally not recommended for surgical intervention and treatment[41,42]. NECs with an Ki-67 index between 20% and 55% have shown low response rates to platinum-based chemotherapy, and there is no standard treatment regimen for these patients[1].

Patients with metastatic NENs of the SB are not excluded from surgery. Several studies have shown an improvement in OS together with control of symptoms following resection of metastatic lymph nodes and liver metastasis. However, these procedures are seldom curative and the recurrence rates at 5 and 10 years are 95% and 99%, respectively[1].

Finally, at the time of surgery for metastatic NENs of the SB, a cholecystectomy should be included due to the high presence of gallstones in patients receiving SSAs[1]. In addition, minimally invasive resection techniques should be performed in younger patients less prone to obstruction, without metastasis, or with small tumors. However, these techniques have limitations that will require surveillance[17].

CONCLUSIONS

Neuroendocrine tumors are neoplasms that can be found in any part of the body. This review is focused on those with a location or origin in the digestive tract at the level of the small intestine due to its variable form of presentation and difficult diagnosis, as well as the treatment approach, emphasizing a multidisciplinary effort. We observed that reports of current series place them in several cases as one of the most frequent tumors in the small intestine. As their incidence is increasing, the importance of understanding their behavior and how to approach them correctly increases. The presence of small bowel NENs results in variable gastrointestinal symptoms, which are frequently a cause of the delay from symptom onset to diagnosis. In addition, a suspected SB NEN must be confirmed by biochemical tests, anatomical and functional images and an anatomopathological study of tissue, the latter preferably carried out by a pathologist experienced in NENs. Each of these will facilitate clinical decision-making. Finally, treatment depends on the extent of the disease; patients with localized disease are considered for surgery and NENs in metastatic stage will be prescribed SSAs, interferon alpha, everolimus or PRRT together with consideration for resection of the primary tumor and cytoreductive surgery. It is necessary to know and understand the behavior, forms of presentation and therapeutic options for NENs of the small intestine in order to improve current patient management.

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MINIREVIEWS

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Abstract

Managing a pandemic is a difficult task. Pandemics are part of the dynamics of nonlinear systems with multiple different interactive features that co-adapt to each other (such as humans, animals, and pathogens). The target of controlling such a nonlinear system is best achieved using the control system theory developed in engineering and applied in systems biology. But is this theory and its principles actually used in controlling the current coronavirus disease-19 pandemic? We review the evidence for applying principles in different aspects of pandemic control related to different goals such as disease eradication, disease containment, and short- or long-term economic loss minimization. Successful policies implement multiple measures in concordance with control theory to achieve a robust response. In contrast, unsuccessful policies have numerous failures in different measures or focus only on a single measure (only testing, vaccines, *etc.*). Successful approaches rely on predictions instead of reactions to compensate for the costs of time delay, on knowledge-based analysis instead of trial-and-error, to control complex nonlinear systems, and on risk assessment instead of waiting for more evidence. Iran is an example of the effects of delayed response due to waiting for evidence to arrive instead of a proper risk analytical approach. New Zealand, Australia, and China are examples of appropriate application of basic control theoretic principles and focusing on long-term adap-

tive strategies, updating measures with the evolution of the pandemic.

Key Words: COVID-19 pandemic; Control; Control theory; COVID zero; Flattening the curve

Core Tip: Controlling an epidemic is a massive challenge due to the nonlinear systems involved and interactions that are hard to model and predict well. Therefore, any pandemic control policy must apply at least the basic principles of control theory, including having multiple measures simultaneously and having models and predictions to combat the time delay between exposure and symptom onset that could lead to loss of life and controllability of the pandemic. In addition, a control-theoretic-based policy needs to factor in a large set of mutual interactions between people, animals, and pathogens that includes media and social networks and their influence on people's behavior, including fake news and the viral spread of disinformation.

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INTRODUCTION

Control theory has been developed for the control of dynamic systems in engineering. Its main principle of feedback control is to use the measurement of the output and/or the states of the system and their deviations from the desired levels or trajectories to reduce the deviations to zero and achieve stability [1]. Although mathematical control theory is being developed to control different engineering processes, dynamic feedback systems are often found in biology at different levels, from cellular to whole organisms[2]. For example, the pituitary axis is involved in hormonal level stability control *via* multiple negative feedback loops to maintain homeostasis under different external stressors from the interactions of the system (the organism) with the environment[3]. Termination of the stress response is one prime example. Sustaining constant levels of different hormones and blood sugar are other examples (blood sugar needs to be at constant levels with the variability of demand for it from various physical and intellectual activities, especially in humans)[3]. Therefore, pandemic control is a natural area of application of control theory to achieve a certain level of disease prevalence, being zero or another appropriate level that does not burden healthcare systems. Sadly, many implemented pandemic control policies are not developed in accordance with the main principles of control theory, leaving suboptimal results and increased incidence of deaths from infectious diseases and financial losses in healthcare systems.

Time delay as a factor in pandemic

One of the main characteristics of an ongoing epidemic is that any implemented measure will have an effect with pure time delay. Even full quarantine that stops transmitting in a matter of a single day will leave many infected people in their incubation periods, who will get sick with an unavoidable delay, depending on it. The presence of asymptomatic transmission as in coronavirus disease-19 (COVID-19) means that if they are not found and isolated in time, they will still be able to transmit it in their households during quarantine - and thus, the measure will have a delay in its effects, which will increase the number of infected, sick, and deceased people[4]. The presence of time delay in a dynamical feedback system leads to old and less usable information in the feedback that has to stabilize it, thus decreasing the stability margins and introducing oscillatory behavior of the output. This is known from the beginning of control theory with the work of James Clerk Maxwell on governors[5].

So, how do we deal with a time delay? One mechanism is with modeling and prediction - making decisions about implementing specific policies at a current level and a projected level. For example, suppose we want to keep the number of occupied hospital beds under a certain threshold. In that case, we do not wait until it is reached to implement the policy. Instead, we rely on modeling and forecast to tell us when it is the last possible moment to implement without reaching it. This approach in Proportional-Integral_Derivative (PID) control uses its derivative part to make linear extrapolations and to use projections to compensate for the older information in the feedback loop due to pure time delay. Stability can be either improved or worsened by predictions. However, too much reliance on the future can decrease stability due to model errors and amplification of noise to signal ratio, just as the derivative part of the PID controller increases high-frequency noises. The future may not happen, and we must be

careful not to base the policy solely on unreliable models with long-term predictions.

Controlling unstable systems

Although the pandemics have been perceived as stable processes that eventually lead to endemic situations, that is not so. Every pandemic brings existential risk to the species that it attacks[6]. Stability can be achieved at a population level as small as zero - far from the desired level that we aim to control. Thus, this system is deemed unstable[7]. The risk of loss of life due to pandemics is fat-tailed. It is worse even than the risk of nuclear war[8,9]. As the history of the plague shows, other possible scenarios, such as endemics, may result in periodic oscillatory behavior without a significant decrease in mortality[10]. Unlike stable systems, an unstable system cannot be left unregulated, so the concept of "no policy" cannot be implemented with the expectation of achieving any measurable results in either death rate, hospitalizations, or economic growth targets. Pandemics must be controlled.

Controlling nonlinear systems

The basic and most often used epidemiological models that capture the dynamics of epidemics are nonlinear. Thus, a system that includes the pathogen and the population has to be considered a nonlinear system.

A significant difference between linear and nonlinear systems is that the principle of superposition does not hold for the latter - the result of a linear combination of inputs is not a linear combination of outputs. In other words, if we put inputs U_1 and U_2 to a system separately and archive outputs Y_1 and Y_2, the result of the input $aU_1 + bU_2$ will not be $aY_1 + aY_2$. This decreases the predictability of the behavior of nonlinear systems. Its direct consequence is that the size of inputs defines a nonlinear system's behavior - doubling the input will not double the output.

Studying the influence of a given set of inputs over the system does not provide us with information for other sets of inputs - we cannot construct the combination of outputs due to the variety of inputs. An example, in pandemic control - implementing policy to decrease the prevalence of a disease depends on the prevalence level - the higher the number of active cases, the longer it will take to reach the desired aim due to the diversity.

WHAT ARE THE MEASUREMENT GOALS IN THE COVID PANDEMIC

Aims of the pandemic control system

To assess proper from improper methods for pandemic control, we need to know what our aim is. Do we want to minimize the lost number of lives? Instead, do we want to keep the healthcare system working and minimize only the collateral damage from the pandemic? Do we want to minimize short-term economic loss of value, or do we want to reduce long-term loss? Do we want to preserve the population's overall health for long-term goals related to spending on healthcare or other incentives to do so?

Any viral pandemic poses risks to the long-term health of a population. For example, children born second or third in a family have substantially increased exposure to respiratory disease than the first-born child, which has long-term consequences for their educational level and labor market outcomes [11]. Similar long-term outcomes were seen with 1918 influenza[12]. Minimizing long-term health damage thus coincides with the number of infected, which controls mostly the number of deceased where no specific treatment is available.

Disease eradication

The goal to eradicate a disease globally is the most ambitious and often includes eradication *via* immunization, as with measles or polio[13]. Although local eradication, as seen in China, can be successful for prolonged periods, the pandemic control policy needs to be adapted continuously to respond to the mutating virus from widespread outside of the country or region that implements the policy[14].

Chinese control policy implements multiple different key elements from control theory to achieve this success, such as early response, traffic control, and predictive mechanisms: Early and rapid response that allows the local reaction to a local cluster without disrupting the socio-economic activity. Delay is the critical variable in the economic costs of any pandemic control strategy - costs increase exponentially over time. Fast and complete isolation of exposed individuals includes extensive data analysis to locate all registered infected contacts automatically, so contact tracing is ahead of the transmission chain. This is the *predictive part* of the control mechanism - who is in incubation and will spread the disease next time? Why is the need for prediction?

Due to asymptomatic spreading in the case of COVID-19, all exposed individuals need to be isolated, which needs to happen before some of them display symptoms to rapidly break the chain of transmissions for up to two incubation periods. For this strategy to work, both in government and people, compliance is needed. Excessive community involvement, government funding, motivation

mechanisms, and constraint mechanisms require serious investment and may be at odds with the political system in a given country, such as data privacy protection policies and traffic restrictions. A control system designed to achieve local zero policy also controls people and their motivation and compliance, which can be expensive and hard to achieve or require actions incompatible with specific legal systems. A high technology approach is also beyond the reach of many countries with smaller budgets for pandemic control.

Although the local disease zero policy is possible and is still successful in China, it has been used before, as in the SARS pandemic in 2003, which was eradicated[15]. It is unstable until global eradication is achieved.

Disease containment

Due to various restrictions in implementing pandemic response, sometimes "flattening the curve" is the main goal - to avoid hospital system overburdening, which can cause excessive deaths due to lack of hospital treatment for other diseases and the infected during the pandemic. This also aims to sustain the long-term quality of healthcare due to the hazardous effects of infections among medics, nurses, and staff and the impact of accumulated fatigue for prolonged periods of overburdening.

Measures and effects

Although different measures suit different regional specifics during a pandemic, countries with multiple standards have seen the most robust outcome[16,17].

This is in line with the basics of control theory - having more degrees of freedom in a controller satisfies many constraints while maintaining stability[18]. Thus, redundancy improves robustness - stability in the face of changing parameters of the system, such as the pathogen transmissibility and severity of disease.

In contrast, in countries with poor outcomes of pandemic control, such as Iran, multiple control mechanisms are broken due to socio-economic conditions, including education, economic disparity, and lack of coherent response from the healthcare community due to limited evidence and scientific controversies, which lead to premature actions from the government towards reopening[19].

Still, when implementing multiple different measures, some key measurements need to be highlighted as high-priority ones.

One very effective non-pharmaceutical intervention for that aim is to localize traffic - reducing interstate traffic in the United States substantially affects deaths and intensive care unit admissions[20]. In addition, the estimation of imported cases shows their significant influence in the case of COVID-19[21].

Another cheaper measure is the use of protection such as masks which are highly effective in decreasing case counts and mortality in multiple different ways, including socio-cultural norms and improvement of long-term behavior during pandemics[22]. For countries with limited budgets, universal mask-wearing must control any respiratory disease pandemic.

Another key and high-priority measure that has a high cost that we already described - rapid response to newly found cases and predictive approach to contact tracing - isolates exposed individuals before they become contagious. This is the golden standard that is difficult to achieve for many already described reasons. However, any effort on contact tracing will impact the health prevention of the infected (early discovery and treatment).

EFFICACY OF PANDEMIC CONTROL MEASURES IN COVID-19 PANDEMIC

When the COVID-19 pandemic began in 2019, precautionary measures started to be taken worldwide to limit the increasing number of cases. However, countries demonstrated that the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) transmission could be gradually retard or stopped. Effective strategies have been developed because the entire scientific and medical community cooperated in identifying cases and developing strategies for diagnoses, therapies, and vaccines. As a result, quick identification of close contacts, and testing and confirming symptomatic and asymptomatic patients have begun. Thus, all institutions' multidisciplinary approaches and collaborative work have led to containment and case management[23].

The main strategies for mitigating the COVID-19 pandemic are based on measures of social distance and health system reinforcement. Many countries have introduced strict lockdowns due to the widespread virus transmission in the community. However, prolonged strict lockdowns have various unfavorable social, economic, and health effects. Permanent lockdowns are not a long-term solution to limiting the COVID-19 pandemic. Lockdowns have reduced the effective reproduction number (R)[24]. But developing all kinds of resources to test and confirm all cases and using other non-therapeutic prevention will prevent SARS-CoV-2 transmission[17,25,26].

Prolonged strict lockdowns can lead to more deaths forward in time and can do more damage than benefits. Not all models analyzing lockdowns consider the potentially possible effects on other diseases. In England and Wales, cardiovascular deaths at home have increased by 35% compared to 2014-2019 [27]. In Italy, mortality from myocardial infarction increased 3 times in March 2020 during the blockade

period compared to the same period in 2019[28]. However, we must consider that lockdowns are not worse than the epidemic. Plenty of literature on the subject shows the effectiveness of lockdowns. Here, the variable that makes a lockdown good or bad is its duration. That is why China makes theirs within 28 d with the help of the strategy described here. An increase in infarcts can be a confounding variable with the disease because it causes such mortality directly and indirectly.

There is also a reduced hospitalization rate for the acute coronary syndrome. The most likely reason is people's fear of infestation with SARS-CoV-2 in hospitals[29,30]. Most of these deaths reported at the time were not due to COVID-19[27]. Children and adolescents are also not spared from the unfavorable effects of lockdowns. The interruption of the educational process and the lack of socialization caused even more problems[31].

The economic effects are expected to lead to rising unemployment and poverty in the long term[32]. Therefore, careful planning is necessary, but the positive results of any decision must exceed the negative effects on the people. Furthermore, all measures must be based on scientific facts and evidence to be as correct as possible to the situation when they are taken to achieve the long-term goal[33].

Hospital preparedness has been one of the main strategies of governments. Still, even the best health care system cannot cope if the viral transmission and infections continue too long. Therefore, increasing the number of beds, adapting infrastructure and redistributing human resources and equipment, implementing measures to protect healthcare staff and patients, and training staff are essential measures to tackle the COVID-19 crisis[34].

In Europe, governments have mobilized special funds to increase labor capacity and equipment. However, even in regions with high resources, such as the USA and Italy, hospitals and intensive care units came under tremendous pressure from the first wave of the disease. There have been situations with difficult decisions to prioritize cases based on patients' age, comorbidities, and health status[35,36]. The hospital overcrowding and pressure on the health care system led to the first lockdown, which imposed severe restrictions on movement worldwide. Therefore, even if significant financial resources were allocated to hospitals' preparation, that would not be enough to mitigate the effects of the pandemic unless other measures are taken.

Initial mortality data were based on confirmed COVID-19 cases, but actual mortality from COVID-19 was established later[37].

A significant part of infected people is undetected because they are asymptomatic or usually do not seek medical attention. In addition, significant differences in the percent of mortality have been found between different age groups[38]. Therefore, many patients with confirmed COVID-19 will not need to be hospitalized, especially the younger ones.

Primary health care can play a crucial role in unburdening hospitals. Previous data have shown that access to family doctors helps treat patients. They can become the first line of defense in diagnosing and preventing COVID-19[39,40]. Thus, severe patients will be referred to hospitals, while those with mild COVID-19 will be treated at home. A well-coordinated and planned process of primary health care will ensure control of the disease spread and identification of vulnerable groups that need to be protected. Early detection of COVID-19, monitoring during isolation, individual risk assessment, treatment of mild COVID-19 cases, and timely identification of worsening conditions could be priorities for family physicians.

Primary healthcare and home care are taken together with more measures that are selective and are the only realistic long-term strategy to mitigate the COVID-19 pandemic.

Controlling the extended pandemic system, with an account for communications impact on behavior, several countries have successfully reduced COVID-19 cases and deaths by maintaining these results for a long time with long-term maintenance of some of the measures related to masks, social distancing, and control of imported cases. The success depends on the reaction and resolution of the governments and how the information has been presented to the public. Unfortunately, there is no universal communication policy for providing information during a prolonged crisis. But if the right, comprehensive, and scientific information reaches the citizens, it also will help control and mitigate the pandemic. Clear and accurate messages made by medical and scientific professionals delivered through appropriate platforms (media, social networks, and other non-government organizations) will ultimately lead to long-term success. But this is a complicated process and much depends on maintaining public confidence.

An overall policy can be outlined, including a communication strategy to refute the available disinformation with scientific data and evidence and different variants to clarify the importance of vaccination programs during the COVID-19 pandemic.

In December 2020, data showed that New Zealand had 420 reported cases and 5 deaths per million population. In the United States, there were 51655 cases and 937 deaths per million. Australia also reported lower numbers for the second week of December 2020 than other European countries - 1094 cases and 35 deaths per million population[41,42].

One of the main factors contributing to Australia's success was its geographical isolation and consensus among political circles and scientific councils on public health about the measures. A multidisciplinary group was formed, including experts from the country's eight leading universities [43]. The aim was to prepare an independent report to acquaint the entire government with the country's situation and give recommendations and guidelines for managing the crisis[44]. They pro-

posed a strategy in which communication in public health is paramount to tackling the pandemic and involves both politicians and communities

There are various recommendations for communication during a crisis. It is imperative to provide specific information on what to do and avoid for certain periods. Clear rules are essential when some restrictions are stringent. There must be absolute consistency in the messages and maximum reliability of the data provided to the public. The field's specialists and scientists should be used, although the public trust in them is not by presumption[45]. Confidence can be quickly lost if the expert is politically committed.

Politicians should listen to the community's needs and concerns when communicating. People are more likely to follow the pieces of advice if they understand the logic behind them. Therefore, explaining why specific actions are critical, beneficial, or problematic is essential. In addition, information concealment can motivate people to look for information elsewhere, promoting belief in rumors, misinformation, and conspiracy theories[46]. There is always uncertainty in crisis management, so there should be no illusion of false security for people because trust will be undermined[47].

People must also be allowed to get involved in the action. This means that communication must be attended to by appropriate measures to favor changes in the behavior and motivation of the population [48]. People are more likely to comply with quarantine if they have the financial and economic resources to endure a period of unemployment. The role of the government is to call for public solidarity and sustainability[49]. Fear and stress are reduced when people are part of a group and are supported. Then work, responsibilities, home life, and even helping others are often at the forefront of their minds.

The outbreak of the COVID-19 pandemic showed another lousy feature of humanity - its lack of faith in science and the scientific community. As a result, we have witnessed the rise of misinformation and conspiracy theories[50,51]. Transparent providing of factual information prevents susceptibility to emerging misinformation and conspiracy.

In combat against misinformation, specific techniques are used to reduce the spread of fake news significantly[52,53]. But again, public trust in government and health institutions is the most important and protective factor against people looking for opportunities for conspiracies[50].

Another critical factor that plays a crucial role in mitigating and controlling the COVID-19 pandemic is vaccination[13,54-58]. Several vaccines have already been approved and available, but vaccination campaigns in some countries are going slowly. It was assumed that the presence of collective immunity would control the pandemic[56]. However, suppose high morbidity, high mortality and adverse economic effects should be avoided. In that case, the vast part of the population must acquire immunity through vaccination but not through past infection. While the global eradication of COVID-19 may prove very difficult to achieve[13,58], successful vaccination programs can focus on regional elimination in the short term. Vaccinations will therefore have a critical impact on the dynamics and management of the COVID-19 pandemic.

If vaccination programs are modeled and combined with disease dynamics and available virus transmission data, a very effective strategy can be obtained that will lead to the successful long-term management of COVID-19. Monitoring, testing, and isolation will remain important factors in controlling the COVID-19 pandemic. Still, the effectiveness of the vaccination program and the level of vaccination will outweigh these factors in eliminating and stabilizing the COVID-19 pandemic.

The proposed approaches to control in all possible directions are not without challenges. We have seen that many factors affect the management of a pandemic. In addition, SARS-CoV-2 is evolving quite rapidly, and the efficacy of the available vaccines against new strains can be much lower. Despite these challenges, the successful implementation of COVID-19 vaccination programs will lead to pandemic control and a return to everyday life.

CONTROLLING IMPORT OF CASES

One of the most important aspects of nonlinear systems is size-dependent behavior. Large systems are inherently harder to stabilize, while smaller systems are much more easily influenced. This explains the hierarchical nature of multicellular organisms with cells, tissues, organs, and systems with separate feedback control mechanisms for different levels[59]. Pandemics are interactions in nonlinear systems comprised of humans, other life forms, and pathogens. A straightforward way to control a pandemic better is to decrease its size. This can mean lowering prevalence in a given area or localizing the pandemics by breaking the dependencies between different world regions. This necessitates control of imported cases. Imported cases can sustain a pandemic even in the absence of local transmission, and failing to account for them will lead to inappropriate responses with measures that are not focused on targeting the imports and exert unnecessary harsh efforts on the community[60]. Controlling imported cases is much easier and more reliable to be done at the borders of a given region instead of doing it after the patient has arrived, which is essential. The latter requires a high-cost, high-tech approach, while the former does not. This is a standard practice in the Chinese response to both pre- and after case imports[61].

CONCLUSION

Although control theory has been developed for engineering, it has found applications in systems biology and pandemic control. It is an abstract, mathematical theory that can be used to analyze and control any dynamic system as long as the calculated measures have the means to be physically applied. The ongoing COVID-19 has been mainly a challenge for epidemiology and pandemic control. It is a novel type of pandemic with multiple different variants emerging consequentially, resulting from the varied responses in other countries and regions and the abandoning of principles of pandemic control in some of them.

However, we know what to do and what not, thanks to management theory and the real-world applications in countries such as New Zealand, China, Australia in zero COVID and Norway, Denmark, Finland, South Korea, and Japan in disease containment. Mathematical modeling has been crucial in pandemic control as means of prediction that allow rapid response to newly found clusters and proper choice of working measures such as social distancing, masks, control of imported cases, *etc.* In addition, localization of pandemic control has been crucial by dividing the world into smaller regions that are easier to manage.

Communication strategies and transparency have helped with compliance and the overall success of non-pharmaceutical interventions. Focusing on long-term health and economic results helped motivate large parts of the industry and the politicians to join the effort. These are the prosperous regions. In policies that fail, multiple causes exist - weak links at the government level and at the social and community levels, including the scientific community that leads to a slow and reactive approach. Measures that are being implemented and lifted too early, lack of consistency with policy, and lack of adaptivity diverged from the basic control theoretic principles.

FOOTNOTES

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Non-medicalization of medical science: Rationalization for future

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Abstract

As we delve into the intricacies of human disease, millions of people continue to be diagnosed as having what are labelled as pre-conditions or sub-clinical entities and may receive treatments designed to prevent further progression to clinical disease, but with debatable impact and consequences. Endocrinology is no different, with almost every organ system and associated diseases having subclinical entities. Although the expansion of these "grey" pre-conditions and their treatments come with a better understanding of pathophysiologic processes, they also entail financial costs and drug adverse-effects, and lack true prevention, thus refuting the very foundation of Medicine laid by Hippocrates "Primum non nocere" (Latin), *i.e.*, do no harm. Subclinical hypothyroidism, prediabetes, osteopenia, and minimal autonomous cortisol excess are some of the endocrine pre-clinical conditions which do not require active pharmacological management in the vast majority. In fact, progression to clinical disease is seen in only a small minority with reversal to normality in most. Giving drugs also does not lead to true prevention by changing the course of future disease. The goal of the medical fraternity thus as a whole should be to bring this large chunk of humanity out of the hospitals towards leading a healthy lifestyle and away from the label of a medical disease condition.

Key Words: Prediabetes; Subclinical hypothyroidism; Osteopenia; Mild autonomous cortisol secretion; Pre-clinical; Medicalization

Core Tip: In this article we discuss several pre-clinical conditions (subclinical hypothyroidism, pre-diabetes, osteopenia, and minimal autonomous cortisol excess), highlighting the futility of early treatment which may not alter the course of future disease. The medical community needs to exercise restraint with pharmacological measures where changes in lifestyle could play a more decisive role in leading a healthy life. Although the expansion of these "grey" pre-conditions and their treatments come with a better understanding of pathophysiologic processes, they also entail financial costs and drug adverse-effects, and lack true prevention, thus refuting the very foundation of Medicine laid by Hippocrates "Primum non nocere" (Latin), *i.e.,* do no harm.

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INTRODUCTION

Background

It was David Humes, who more than 250 years ago had discerningly said that "It is impossible to separate the chance of good from the risk of ill", an adage that holds even more meaning today than ever before. In today's era of rapid progress in medical science, the lines have been blurred between "ease" and "dis-ease" with not only medical terms for pre-clinical medical conditions but also various pharmacological treatments being encouraged to "prevent" the development of clinical diseases. The rationale for such treatments remains debatable and controversial.

The concept of medicalization dates back to 1968 when Zola[1] (1972) defined medicalization as "an effective means of social control". Thereafter, Conrad, one of the pioneers of medicalization, defined it as a "process by which non-medical problems become defined and treated as medical problems, usually in terms of illness and disorders"[2]. As a continually evolving term over decades, medicalization can range from sexuality to garden variety mood disturbances, from childbirth to menopause, from cancer to ageing, blurring the lines between physiological and disease states. While physicians' social movements used to be at the crux of medicalization when it was first introduced as a concept in the 1970s, the major players driving medicalization today have been the pharmaceutical and biotechnology industries, posing ethical concerns. The other main reason is the urge to find something "new" or target newer/higher/lower goals in therapeutics by medical scientists, leading to a flurry of pre-clinical labels to almost every chronic disease.

In this article we discuss a few of these pre-clinical conditions [subclinical hypothyroidism, pre-diabetes, osteopenia, and minimal autonomous cortisol excess (MACS)], highlighting the futility of overtreatment which may be variable early in the course. The medical community needs to exercise restraint with pharmacological measures where changes in lifestyle could play a more decisive role in leading a healthy life.

SEARCH STRATEGY

The following databases were used to identify the relevant studies: PubMed/Medline, Scopus, and Cochrane databases. We also applied RCA (Reference Citation Analysis) to further enhance our search results. All the databases were searched from their inception till March 10, 2022. We did a search again and the search was extended up till June 10, 2022 to look for any additional articles. Keywords used were mainly related to the topics of interest including "prediabetes" or "impaired fasting glucose" or "impaired glucose tolerance", "subclinical hypothyroidism", "osteopenia" or "low bone mass", and "mild autonomous cortisol excess". Reference lists of review articles and guidelines were also scanned for potential articles for inclusion. There was no restriction for study design and language (where English language translation was available). All articles related to non-medicalization were reviewed and those relevant to the topics of interest were considered for inclusion in this scoping review.

MACS

MACS is defined as adrenocorticotropic hormone independent cortisol excess often without clinical signs and symptoms of Cushing's syndrome. Previously referred to with terms including "subclinical Cushing's syndrome", "preclinical Cushing's syndrome", and "subclinical hypercortisolism", currently the European Society of Endocrinology/European Network for the Study of Adrenal Tumors has suggested the use of the term "minimal autonomous cortisol excess" which is universally used[3]. The

term was first introduced as "Pre-clinical Cushing's syndrome" by Charbonnel and coworkers in 1981 [4]. The entity has since made rapid strides and undergone major changes with respect to its understanding, nomenclature, and definitions used for diagnosis.

Approximately 0.3% of adrenal incidentalomas present with Cushing's syndrome[5]. MACS is diagnosed in 5%-48% of patients with incidentally discovered adrenal tumors following evaluation in endocrine clinics[6,7]. The diagnosis of MACS is made in patients with adrenal incidentaloma by an abnormal 1-mg dexamethasone suppression test (DST) with absent stigmata of Cushing's syndrome. The 1-mg DST has been recommended by current recommendations to have the highest sensitivity for diagnosing MACS[3,8]. However, the diagnosis requires exclusion of potential causes of physiological hypercortisolism such as obesity, diabetes, and anxiety/depression. These have also been described as comorbidities associated with MACS and can act as potential confounders in diagnosis.

In a recent systemic review and meta-analysis done by Elhassan *et al*[9] involving more than 4000 patients with benign adrenal incidentalomas, the prevalence of hypertension, obesity, dyslipidemia, and type 2 diabetes in the MACS sub-group was 64%, 41%, 34%, and 28% respectively. This prevalence of dyslipidemia and obesity was almost similar to that of non-functioning adrenal tumors (NFAT) and only hypertension and diabetes were more common in the MACS subgroup. Although hypertension, dyslipidemia, and diabetes were likely to worsen in the MACS sub-group on follow-up, progressive worsening is the *sine qua non* in most chronic conditions. The results have been conflicting with cardiovascular events being prevalent in non-functioning adrenal tumors at baseline (8.7% *vs* 6.3%), and new cardiovascular events developing in MACS than NFAT (15.5% *vs* 6.4%). On top of it, the mortality rates were similar between the two groups despite these differences in metabolic complications. This would mandate a cautionary approach to managing "mild" hypercortisolism based on no difference shown in mortality outcomes, thus putting in doubt the benefit of any intervention at this so-called pre-clinical stage

Patients with MACS have also been found to carry a risk of osteoporosis and mostly asymptomatic vertebral fractures (46%-82%), as compared to 13%-23% of patients with non-functioning adrenal incidentalomas[10]. A study done by Goh *et al*[11] followed 101 patients with benign adrenal adenomas over a 3-year follow-up period. Ninety-two patients had a diagnosis of non-functioning adenomas while nine had a diagnosis of MACS defined as an abnormal 24-h urinary free cortisol and 1mg-DST. After 3 years (range 2.9-4.7 years), four of the nine patients with MACS showed normalization of cortisol parameters (44%), and five of the 92 non-functional AI patients developed MACS (5%). Nearly half of the patients with MACS had normalization of biochemical parameters on follow-up. Whether the initial diagnosis was because of a false-positive test in the first place, or a spontaneous reversal of the cortisol excess, the more important fact is that only 9% of patients had MACS initially and more than half of them normalized on follow-up. Additionally, the risk of progression to overt Cushing's remains very low (< 1%) in patients with MACS, as has been uniformly reported across multiple studies[12-14]. Hence, this should prompt a more vigilant interpretation of any results which imply a higher risk for complications in MACS. This also suggests that caution be exercised with regard to diagnostic interpretation and adopting invasive management decisions.

There remains a need to establish the benefits of adrenalectomy with regard to mortality, quality of life, and potential reversal of these comorbidities in light of the doubtful clinical impact of MACS. A meta-analysis done by Bancos *et al*[15] involving retrospective studies with heterogeneous definitions of MACS showed improvement in hypertension (relative risk [RR] = 11, 95%CI: 4.3–27.8) and diabetes mellitus (RR = 3.9, 95%CI: 1.5–9.9), but not dyslipidemia (RR = 2.6, 95%CI: 0.97–7.2) or obesity (RR = 3.4, 95%CI: 0.95–12) when compared with conservative management. A study done by Salcuni *et al*[16] found a 30% vertebral fracture risk reduction with surgical *vs* conservative management (odds ratio = 0.7, 95%CI: 0.01-0.05, P = 0.008). There have been few studies on the potential use of Mifepristone and Metyrapone in MACS demonstrating beneficial effects on several metabolic parameters[17,18].

All such evidence is largely based on small, heterogeneous studies with inconsistent definitions of MACS and comorbidities as well as degrees of improvement. With the knowledge that half of MACS cases return to normalcy (nonfunctional status), < 1% progress to Cushing's syndrome, and a major surgery involves risks and morbidity, publication bias for positive results certainly calls into question this medicalization.

Moreover, differences in assay factors and the presence of significant comorbidities may lead to possible false-positive results leading to misclassification of patients and adding to bias.

The 2016 European guidelines for the management of adrenal incidentaloma currently suggest an individualized approach. They do recommend surgical management in patients with post-dexamethasone cortisol > 138 nmol/L (> 5 μg/dL) and the presence of at least two comorbidities potentially related to cortisol excess (*e.g.*, type 2 diabetes, hypertension, obesity, and osteoporosis), of which at least one is poorly controlled by medical measures. One needs to weigh the risks and morbidity associated with an adrenal surgery with the perceived benefits. A causal link between MACS and these comorbidities has not been unequivocally established, and these comorbidities can usually be efficaciously managed with medical treatment. Robust randomized trials comparing intensive medical therapy and adrenalectomy, with consistent definitions, appropriately defined endpoints, and a longer duration of follow-up, may bust the myth of operating on MACS.

Subclinical hypothyroidism

As an entity which has been in vogue over the past few decades, subclinical hypothyroidism is essentially a biochemical diagnosis, defined as an elevated thyrotropin (TSH) level with a fT4 level that is within the population specific range.

The prevalence of overt hypothyroidism ranges from 0.2%-5.3%[19] while the prevalence of subclinical hypothyroidism varies from 4.3% to 15% (3× to 150×), with a multitude of factors affecting incidence, including female gender, age, and iodine status[20]. Serum TSH levels in subclinical hypothyroidism have been classified into two categories ranging from the upper limit of normal to 10 and 10 or higher. What is interesting to note is the fact that more than 90% of patients fall in the earlier bracket. Even more striking is the fact that the risk of progression to overt hypothyroidism is only 2% per year in the absence of thyroid peroxidase (TPO) antibodies and 4% per year in the presence of TPO antibodies. As many as two-thirds (approximately 60%) of these individuals see their TSH levels return to the normal range without treatment[21]. Simply put, treating 100 patients for hypothyroidism with TSH between 4-10 mU/mL will potentially avoid progression to overt hypothyroidism in 2-4 patients while what they add on to are unnecessary multiple clinic visits, treatment costs, polypharmacy, and modification of daily habits including taking the tablet 30-60 min before a meal in the rest. The question that matters "is it really worth it?" and are we wasting 96% of our efforts? Would it not be prudent to wait for identifying and then treating only those who actually progress to overt hypothyroidism unless there are significant immediate medical concerns which may benefit from treatment as in infertility or in pregnant females?

There are a number of factors affecting TSH levels. TSH levels tend to follow a circadian fluctuation with nadir levels in the afternoon and only 30% having higher levels in the evening and night. This TSH peak may also be altered in night-shift workers and those with irregular sleep patterns, following vigorous exercise, and mood disorders. Moreover, although population specific reference ranges have been defined for fT4 and TSH concentrations, the intra-individual hypothalamic-pituitary axis set point is largely genetically determined and is minutely sensitive to changes in thyroxine concentrations, which despite being within the population specific range, may be enough to result in an increased TSH concentration. Furthermore, due to alterations in the hypothalamic-pituitary TSH set point, there is a trend towards elevated TSH concentrations with advancing age which is a physiological change. Besides this, there are several conditions which should be ruled out before making a diagnosis of subclinical hypothyroidism (SCH)[22] (Table 1).

Taking these factors into account, the guidelines clearly mention that a diagnosis of subclinical hypothyroidism should be made following confirmation with a repeat TSH and T4 measurement[23] and even when reconfirmed on second testing, only a subset may need treatment. However, one-third of the people are offered treatment after a single TSH measurement making them "patients" and making levothyroxine one of the leading prescriptions worldwide[24].

Symptoms and quality of life: With regard to symptomatology, around one in three patients with subclinical hypothyroidism are asymptomatic. Symptoms when present, tend to predominantly be fatigue, muscle weakness, and cold intolerance. However, around 20%-25% of patients with normal TSH levels report these symptoms. A meta-analysis done by Feller *et al*[25] in 2018 on quality of life showed no difference in hypothyroid symptoms (16.7 *vs* 16.5) or fatigue (28.6 *vs* 29) as assessed using the ThyPRO self-reported instrument (scale 0–100, lower better), or in health related quality of life, depression, cognitive function, or muscle strength. About treatment on the various aspects of hypothyroidism, the largest trial done to date, the TRUST trial, did not demonstrate any effect of levothyroxine on the coprimary outcomes of hypothyroid symptoms and fatigue scores after 12 mo of therapy nor on the secondary outcomes of quality of life, handgrip strength, cognitive function, blood pressure, weight, body mass index (BMI), waist circumference, or carotid plaque thickness[26].

Cardiovascular risk: Amongst the various organ systems that thyroid hormone does play a role in, its effects on the cardiovascular system have been evaluated most extensively. Multiple studies have found that surrogate markers of cardiovascular function (such as left ventricular diastolic function) and lipid profile deteriorate with subclinical hypothyroidism[27,28]. However, while these observations seem to suggest that raised TSH levels may be associated with an increased risk of adverse cardiovascular outcomes, such has not been the case in multiple randomized trials. Subclinical hypothyroidism was not associated with an increased risk of atrial fibrillation, heart failure, stroke, coronary heart disease events, mortality from coronary heart disease, or overall mortality compared with euthyroid individuals in an individual patient meta-analysis performed by the Thyroid Studies Collaboration[29-32]. There are limited randomized clinical trials with sufficient power to examine the impact of thyroid hormone therapy on cardiovascular events, and the TRUST study found that treatment of SCH did not impact the incidence of cardiovascular events within 1 year after initiation of therapy[26].

Treatment: Current guidelines recommend that all individuals with subclinical hypothyroidism would not benefit from treatment and clinicians need to weigh other factors when deciding on treatment[33-35]. Treatment guidelines for subclinical hypothyroidism have been summarized[36-38]. To conclude, there is significant evidence to suggest that subclinical hypothyroidism remains an entity which is

Table 1 Causes of elevated thyrotropin levels

Transient increase in TSH	Permanent increase in TSH
Non-thyroidal illness	Assay interference
Thyroiditis	TSH hormone resistance
Medications: Amiodarone and Lithium	Adrenal insufficiency
Lack of adherence to treatment	Obesity

TSH: Thyrotropin.

misdiagnosed and largely over-treated, and there is a need to improve adherence to the guidelines (Table 2) with periodic reassessment of symptoms, with discontinuation of treatment if and when no benefit becomes evident.

Prediabetes

Pre-diabetes, a term developed to pre-empt the progression to diabetes, represents an intermediate state of hyperglycemia. Varying definitions have been used by the World Health Organization (WHO) and the American Diabetes Association (ADA) to define prediabetes, classifying them into impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) depending on fasting plasma glucose levels and 2-h plasma glucose levels after a 75 g oral glucose tolerance test. ADA, in addition, uses hemoglobin A1c (HbA1c) too to classify diabetes[39,40].

The worldwide prevalence of diabetes ranges from 6% to 10.5% in adults[41,42] while the prevalence of pre-diabetes ranges from 5.5% to around 50%[43] depending on the ethnicity and definitions used to define pre-diabetes (Table 3). The yearly conversion rate from pre-diabetes to diabetes is 5%-20%, with rates ranging from 4%-6% for isolated IGT, 6%-9% for isolated IFG, and 15-19% for those with both IFG and IGT[44]. The reversal rates vary from 45% for individuals with IFG, 37% for individuals with IGT, and 17% for individuals with impaired HbA1c levels[45].

Complications of pre-diabetes: The strongest evidence for pre-diabetes comes with cardiovascular complications[46]. In a meta-analysis done by Huang *et al*[47], IFG, IGT, and HbA1c were independently associated with an increased risk of composite cardiovascular outcomes, coronary heart disease, stroke, and all-cause mortality. In a meta-analysis done by Echouffo-Tcheugui *et al*[48], pre-diabetes was associated with a moderately increased risk of CKD. Several studies have shown similar results with increased rates of micro-albuminuria and progression to chronic kidney disease in prediabetes[49-51]. Pre-diabetes also has been associated with an increased prevalence of diabetic neuropathy, especially autonomic involvement, and increased risk of diabetic retinopathy[52,53].

Treatment: Multiple randomized control trials including the diabetes prevention program (DPP)[54], the Finnish diabetes prevention study[55], and the Da Qing diabetes prevention study[56] demonstrated that lifestyle/behavioral therapy is highly effective in preventing progression to type 2 diabetes. In a recent meta-analysis, lifestyle interventions for obese or overweight individuals with pre-diabetes led to a reduced incidence of diabetes[57]. The DPP for instance demonstrated that an intensive lifestyle intervention could reduce the risk of incident type 2 diabetes by 58%. To prevent one case of diabetes during a period of 3 years, 6.9 persons would have to participate in the lifestyle-intervention program, and 13.9 would have to receive metformin. The ADA currently recommends lifestyle modification for pre-diabetes with a target of 7% weight loss and 150 min/wk of moderate intensity physical activity[58].

While weight loss does lead to a definite reduction in incident type 2 diabetes, it often comes with the challenge of sustaining it long-term[59]. Multiple pharmacological agents have been evaluated with the strongest evidence and long-term safety favoring metformin. In the Indian Diabetes Prevention Programme (IDPP-1) study, metformin and lifestyle intervention reduced diabetes risk similarly at 30 mo although the lifestyle intervention in the Indian DPP-1 was less effective than the DPP[60]. The ADA currently recommends that metformin should be considered in those with BMI ≥ 35 kg/m^2, those aged < 60 years, and women with prior gestational diabetes mellitus[58].

While current evidence does suggest the effectiveness of treatment modalities for the prevention of pre-diabetes to diabetes, the long-term effects on microvascular and macrovascular complications remain debatable. Moreover, although pharmacotherapy has been found to be beneficial in preventing type 2 diabetes, questions regarding the starting and endpoint of therapy, long-term safety of other potential drugs, and economic considerations regarding its cost-effectiveness and health benefits remain unanswered.

Shahraz *et al*[61] using NHANES data showed that a widely promoted web-based risk test by ADA and AMA would label more than 73 million Americans, including more than 80% of those older than 60 years, as being at high risk for "prediabetes", thus elegantly demonstrating how common conditions can

Table 2 Guideline recommendations for treatment of subclinical hypothyroidism

Degree of subclinical hypothyroidism	ATA 2012[36]	ETA 2013[37]	NICE 2019[38]
TSH > 10 mIU/L	Levothyroxine should be considered. (Grade B)	Younger patients (< 65 to 70 yr): Treatment with levothyroxine is recommended, even in the absence of symptoms. (Grade 2); Older patients (> 70 yr): Treatment with levothyroxine should be considered if clear symptoms of hypothyroidism are present or if the risk of vascular events is high. (Not a graded recommendation, but part of the treatment algorithm)	All adults (on 2 occasions, 3 mo apart) consider treatment.
TSH: ULN to 10 mIU/L	Treatment should be considered on the basis of individual factors (*i.e.*, symptoms suggestive of hypothyroidism, a positive test for antibodies to thyroid peroxidase, or evidence of atherosclerotic cardiovascular disease, heart failure, or associated risk factors for these diseases). (Grade B, because of a lack of randomized, controlled trials)	Younger patients (< 65 to 70 yr): A trial period of treatment with levothyroxine should be considered when symptoms suggestive of hypothyroidism are present. (Grade 2); Older patients (especially > 80 to 85 yr): Careful follow-up with a wait-and-see strategy, generally avoiding hormonal treatment, is recommended. (Grade 3)	Age < 65 years (on 2 occasions, 3 mo apart): Consider a 6-mo trial of levothyroxine if symptoms are present.

ATA: American Thyroid Association; ETA: European Thyroid Association; NICE: National Institute for Health and Care Excellence; TSH: Thyrotropin.

Table 3 Criteria for prediabetes

	WHO[39]	ADA[40]
FPG (mg/dL)	110-125	100-125
2-h plasma glucose (mg/dL)	140-199	140-199
HbA1c (%)		5.7-6.4

ADA: American Diabetes Association; FPG: Fasting plasma glucose; HbA1c: Hemoglobin A1c; WHO: World Health Organization.

be "medicalized".

Osteopenia

Osteopenia, a term which came into being by the WHO in 1992, was initially "meant to indicate the emergence of a problem without having any diagnostic or therapeutic significance". The WHO currently defines osteopenia as a bone mineral density (BMD) T score that is higher than −2.5 but less than −1.0[62,63].

The prevalence of osteoporosis ranges from 2% to 26.3%[64] while that of osteopenia is two to three times higher, varying from 54% to 80%[65]. Because osteopenia is so much more prevalent than osteoporosis, the majority of fractures occur in women with osteopenia. In the National Osteoporosis risk assessment study which involved 149542 postmenopausal women followed for 1 year, the gross disparity in the proportion of women with osteopenia and osteoporosis (39% *vs* 6%) meant that more fractures were observed among women with osteopenia despite that they had a lower risk for the same.

When we look at the temporal transition of osteopenia to osteoporosis in a study done by Gourlay *et al*[66] which included 3702 women with osteopenia, the investigators estimated the time for 10% of the women to transition to osteoporosis before having a hip or clinical vertebral fracture. Women were stratified into three subgroups: Mild osteopenia (T score from −1.01 to −1.49), moderate osteopenia (T score from −1.50 to −1.99), and severe osteopenia (T score from −2.00 to −2.49). For 10% of the women to transition to osteoporosis, it took 17 years for those with mild osteopenia, 5 years for those with moderate osteopenia, and 1 year for those with severe osteopenia. Moreover, there was no difference in time needed to transition to osteoporosis among women with normal bone density and mild osteopenia.

Hillier *et al*[67] performed a study including a large cohort of women aged 65 years and older with osteopenia at baseline; 4.7% and 15.7% of these women developed hip and a major osteoporotic fracture, respectively, within 10 years. The corresponding values were 1.2% and 6.3% for women with normal BMD and 14.3% and 30% for women with osteoporosis.

While lifestyle measures along with appropriate intake of calcium and vitamin D can be uniformly recommended to all women with osteopenia, pharmacological treatment remains largely debatable[68,69]. A variety of algorithms and clinical tools such as the fracture risk assessment tool have been developed to enable physicians in stratifying women with osteopenia and decide on potential indications of treatment. Most trials evaluating the efficacy of these agents involve women with

Table 4 Criteria for defining osteopenia

Category	Definition	Treatment recommendation
"Moderate risk", Endocrine Society guidelines 2019[74]	Clinical: No prior hip or spine fractures, BMD T-score at the hip and spine both above -2.5, 10-yr hip fracture risk < 3% or risk of major osteoporotic fractures < 20%	Reassess fracture risk in 2-4 yr. Country-specific guidelines for treatment
ISBMR guidelines 2021 [75]	BMD T-score between -1.0 and -2.5 at the femoral neck or lumbar spine, 10-yr probability of a hip fracture ≥ 3.5%, or a 10-yr probability of a major osteoporosis-related fracture ≥ 10.5% based on the FRAX tool (based on limited data in Indians)	Advisable to initiate treatment

BMD: Bone mineral density.

osteoporosis or prevalent vertebral fractures with fewer trials in osteopenic women. In the fracture intervention trial, alendronate was not associated with a reduced risk of sustaining a vertebral fracture among women with a T score between −1.6 and −2.5 (hazard ratio = 0.8; 95%CI: 0.3–2.1)[70]. In a RCT done by McCloskey *et al*[71], the number needed to treat (NNT) to prevent the occurrence of one clinical fracture was three and a half times higher among women with T>-2.5 than women with osteoporosis (NNT = 66 *vs* 19) despite a similar RR reduction (22% *vs* 30%). Hence, while RR reduction might appear greater in terms of numbers, it does not quite translate into significant numbers in terms of absolute risk reduction. Cost-effectiveness is another factor that needs to be taken into consideration. Studies done by Schousboe *et al*[72] and Meadows *et al*[73] have assessed the cost-effectiveness of prescribing alendronate among post-menopausal women with osteopenia and found that the drug is not cost-effective. The long duration of treatment, lack of defined endpoints, and the adverse effects associated with long-term use are other factors that need to be considered prior to initiating pharmacological therapy in osteopenia (Table 4)[74,75]. Hence, in the absence of unequivocal clinically and epidemiologically relevant benefits of pharmacotherapy, osteopenia essentially remains a radiological diagnosis in the absence of risk factors for fracture and is probably best managed by periodic monitoring and fracture risk assessment.

Reasons for progressive medicalization

There are many reasons why clinicians may provide more care than is needed. A primary reason is "technology creep". After a new drug or device is approved for use in a condition in which there is a proven benefit, its use often expands to lower-risk groups in which the benefit does not outweigh the risk. Others include payment systems that reward procedures disproportionately compared with talking to patients, expectations of patients who equate testing and interventions with better care, the glamour of technology, the fact that it may be quicker to order a test or write a prescription than explain to a patient why they are not being treated, and defensive medicine[76]. Even if a medical intervention has been shown to provide a clear benefit in selected groups, using it in other groups, especially in those with milder disease or at-risk group for disease, can result in harm.

It is worthwhile to note that providing excessive health care service is most likely to occur in situations in which there is less strong evidence to document the benefit and harms of the service. In fact, editors of *JAMA Internal Medicine* took note of "medicalization" of common conditions, as an area of increasing concern[77]. "Less is More" was a series used to highlight situations in which the overuse of medical care could result in harm and in which less care is likely to result in better health[78]. A comprehensive look at the four pre-clinical conditions is summarized in Table 5.

CONCLUSION

A fine balance between indiscriminate acceptance of medicalization of areas of human existence and blind criticism of new medicalization cases needs to be struck. A reasonable way to look at any chronic non-communicable disease should be to avoid unnecessary medicalization by medical labeling of the "grey zone" preceding a disease. Rather, it should seek to identify people at the highest risk for targeted allocation of limited health care resources and address the lifestyle changes which can improve the overall health of the community. Having a proven therapeutic intervention for a disease does not pre-validate its use in the pre-clinical stage of the same disease and can lead to more harm than good.

The time is more than ripe for paying heed to hard facts and sane logic both for the patient as well as the medical community for treading carefully with regard to early interventions for "preclinical and subclinical" conditions in medical science.

Table 5 Clinical spectrum of preclinical conditions: Looking at hard facts

	Prediabetes	Subclinical hypothyroidism	Osteopenia	MACS
Clinical disease	Diabetes	Overt primary hypothyroidism	Osteoporosis	Cushing's syndrome
Prevalence of preclinical condition	5.5%-53.1%[43], IFG - 6.2%[41], IGT -10.6% [41]	4.3%-15%[20]	54%-80%[65]	5%-48%[6]
Prevalence of clinical condition	10.5%[41]	0.2%-5.3%[19]	2%-26.3%[64]	0.3% of patients with adrenal incidentalomas[5]
Dx criteria	FPG: 100-125, 2-h PPG: 140-199, HbA1C: 5.7-6.4	Elevated TSH level with a fT4 level that is within the population specific range	T-score between -1 to -2.5	Abnormal 1-mg dexamethasone suppression test with absent stigmata of Cushing's disease.
Progression	5%-18.3%[54,55,60]	2%-6%[22]	16% risk of major osteoporotic fracture in 10 years [67]	< 1%[13]
Regression/reversal	19%[54]	60%[21]	Stays static or progresses	2%-44%[6,11]
Long-term sequelae	Microvascular and macrovascular complications of diabetes, Cardiovascular risk	Markers of cardiovascular function (such as left ventricular diastolic function) and lipid profile deteriorate with subclinical hypothyroidism	Fractures	Hypertension, Diabetes, Dyslipidemia, Osteoporosis
Short-term consequences		Fatigue, muscle weakness, cold intolerance		
Preventive options	Lifestyle and behavioural therapy, drugs	Lifestyle and behavioural therapy, drugs	Lifestyle and behavioural therapy, drugs	Lifestyle and behavioural therapy, drugs, surgery
Pharmacotherapy	Metformin	L-thyroxine	Calcium and vitamin D	Mifepristone, metyrapone
Surgery	-	-	-	Adrenalectomy
True prevention	x	x	x	x
Adverse effects of treatments available	B12 deficiency	Bone loss, cardiac arrhythmias in elderly	Overtreatment can predispose to hypervitaminosis D	Hypocortisolism
Recommendations/Guidelines	Metformin should be considered in those with BMI ≥ 35 kg/m^2, those aged < 60 yr, and women with prior gestational diabetes mellitus with IGT	TSH > 10 mIU/L, consider treatment; TSH < 10 mIU/L, consider treatment if symptoms suggestive of hypothyroidism, positive antibodies to thyroid peroxidase, or evidence of atherosclerotic cardiovascular disease, heart failure, or risk factors for these diseases	Country-specific guidelines for treatment	Individualized approach to consider patients with 'autonomous cortisol secretion' due to a benign adrenal adenoma and comorbidities potentially related to cortisol excess for adrenal surgery
Grade of recommendation	Level of evidence A[58]	Grade B, BEL 1 (Best evidence rating level)[36]	-	(⊕OOO) Very low level of evidence/recommendation[3]

MACS: Minimal autonomous cortisol excess; IFG: Impaired fasting glucose; IGT: Impaired glucose tolerance; FPG: Fasting plasma glucose; HbA1C: Hemoglobin A1c; PPG: Photoplethysmography; TSH: Thyrotropin; BMI: Body mass index.

FOOTNOTES

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ORIGINAL ARTICLE

Observational Study

Migraine in physicians and final year medical students: A cross-sectional insight into prevalence, self-awareness, and knowledge from Pakistan

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Abstract

BACKGROUND

Despite its high prevalence, migraine remains underdiagnosed worldwide. A significant reason is the knowledge gap in physicians regarding diagnostic criteria, clinical features, and other clinical aspects of migraine.

AIM

To measure the knowledge deficit in physicians and medical students and to assess the prevalence of migraine in the same population.

METHODS

An online questionnaire was developed and distributed among physicians and final year medical students on duty in various medical and surgical specialties of Allied and DHQ Hospitals, Faisalabad, between October 2018 and October 2019. Inclusion criteria were public practicing physicians who experience headaches, while those who never experienced headaches were excluded. Different questions assessed respondents on their knowledge of triggers, diagnosis, management, and prophylaxis of the migraine headache. They were asked to diagnose themselves using embedded ICHD-3 diagnostic criteria for different types of migraine.

Graphs, tables, and figures were made using Microsoft Office 2016 and Microsoft Visio, and data analysis was done in R Studio 1.4.

RESULTS

We had 213 respondents and 175 fulfilled inclusion criteria, with 99 (52%), 58 (30%) and 12 (6.3%) belonging to specialties of medicine, surgery, and others, respectively. Both genders were symmetrically represented (88 male and 87 female). Fifty-two (24.4%) of our 213 respondents were diagnosed with migraine, with 26 (50%) being aware of it. Females had higher prevalence among study participants (n = 28, 32.2%) compared to males (n = 20, 22.7%, P = 0.19). A majority (62%) of subjects never consulted any doctor for their headache. Similarly, a majority (62%) either never heard or did not remember the diagnostic criteria of migraine. Around 38% falsely believed that having any type of aura is essential for diagnosing migraine. The consultation rate was 37% (n = 65), and migraineurs were significantly more likely to have consulted a doctor, and a neurologist in particular (P < 0.001). Consulters and migraineurs fared better in the knowledge of diagnostic aspects of the disease than their counterparts. There was no significant difference in other knowledge aspects between consulters *versus* non-consulters and migraineurs *versus* non-migraineurs.

CONCLUSION

Critical knowledge gaps exist between physicians and medical students, potentially contributing to misdiagnosis and mismanagement of migraine.

Key Words: Migraine; Headache disorders; Knowledge study; Prevalence; Knowledge; Epidemiology; Public health

Core Tip: Despite its high prevalence, migraine remains underdiagnosed worldwide. A significant reason is the knowledge gap in physicians regarding diagnostic criteria, clinical features, and other clinical aspects of migraine. The primary objectives of this study were to measure the knowledge deficit in physicians and medical students and to assess the prevalence of migraine in the same population.

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INTRODUCTION

Headache is the top neurological complaint of patients presenting to general practitioners and neurologists. Migraine, one of the commonest headaches, is the sixth most prevalent disease globally and the second largest cause of disability, affecting more than 1 billion people[1,2]. Although not directly fatal, migraine results in considerable loss of work hours, productivity, and quality of life, culminating in a health burden and significant cost. In the United States alone, the annual expenditure on migraine exceeds 78 billion USD[3]. Despite being one of the top causes of morbidity, millions of migraine cases remain undiagnosed worldwide, leading to a preventable burden on the system[4]. This underdiagnosis has been attributed to lapses in physicians' knowledge and lack of patient consultation, besides various other factors[5,6]. A recent study published in 2021 revealed several knowledge gaps in primary care providers concerning migraine diagnosis, with only 6.3% of physicians aware of migraine prevention guidelines[7]. Studies have elucidated a significantly higher prevalence of migraine in physicians, attributed to the better knowledge of diagnostic criteria and a variety of presentations of this headache[8]. Studies have also shown a specifically higher prevalence of migraine in headache specialists (53% compared to 19.3% in general practitioners), relating it to a better knowledge of the diagnostic criteria of migraine[9].

Prevention is the key management strategy for a significant subset of the population experiencing migraines, particularly those who cannot take abortive treatment. Preventive strategies, including drugs, indications of prophylaxis, and avoidance of triggers, constitute an essential piece of knowledge for managing physicians in this regard. Some of the triggers of migraines may not be commonly known

by physicians, leading to incomplete medical advice and counseling. Studies have shown a significant difference in the discussion of migraine triggers (with the patients) among neurologists and other physicians (82% *vs* 51%)[10]. Only a physician adequately equipped with proper knowledge of prevention and triggers can manage migraine patients properly with a comprehensive education of prevention strategies. Lack of awareness of triggering factors among patients increases the frequency of otherwise avoidable exacerbations of migraine[11].

Pakistan's estimated 1-year prevalence of migraine (22.5%) is considerably higher than the global 1-year prevalence of 15%[12,13]. Headache patients present in the outpatient settings of multiple specialties of our hospitals, including surgery. Junior doctors (including sub-interns, *i.e.*, final year medical students) in Pakistan's public hospitals serve as the first contact with health care for most patients with headaches. Therefore, the knowledge, attitudes and practices related to headache serve a pivotal role in the accurate and timely diagnosis and management of patients with headache syndromes, including migraine. Knowing the types of migraines and diagnostic criteria, and screening tools for some common types are essential for correct diagnosis. Transient neurological disturbances, usually in the form of visual or auditory sensory issues that precede migraine headaches, are known as auras. Aura is not experienced by 60%–80% of migraine patients, leading to a diagnosis of migraine without aura[14]. Worldwide, some studies recently have highlighted the gaps in physicians' knowledge regarding the diagnosis of migraine[5,15,16]. We hypothesize similar gaps exist in our clinical settings in Pakistan; viewing aura as an integral part of the diagnosis of migraine being one such gap in knowledge. It is imperative for physicians to be aware of migraine without aura as it constitutes > 70% of migraine cases in Pakistan[17].

The aim of the study was to provide the first insight in the region into physicians' knowledge regarding the diagnosis and management of migraine. The primary objective was to gauge the knowledge of physicians and final-year medical students regarding the triggers, diagnosis, management and prevention of migraine in Pakistan. Secondary objectives included determining the awareness of their own migraine among migraineurs, as well as estimating the point-prevalence of migraine among the physician population in Pakistan. Moreover, we also sought an assessment of the attitudes of our respondents towards medical consult-seeking for their headaches and self-medication (without a medical consult).

MATERIALS AND METHODS

Study design

A web-based 30-question anonymous questionnaire was developed consisting of simple multiple choice as well as multiple choice–multiple response questions.

Participants

The questionnaire was distributed among physicians and final year medical students on duty in various medical and surgical specialties of Allied and DHQ Hospitals, the affiliated hospitals of Faisalabad Medical University. Participants were required to fill in the questionnaire in the presence of a team member to avoid misinterpretation of any question.

Inclusion criteria and data collection

Inclusion criteria were physicians and final year medical students who experienced headaches. Private practitioners and non-practicing physicians were excluded. The data were collected between October 15, 2018 and October 15, 2019.

Tools and variables

Respondents were asked if they thought they had a migraine and were then assessed on their knowledge of the definition, triggers and prophylaxis of the migraine, utilizing various subjective and objective questions. The triggers of migraine and the list of indications of prophylaxis of migraine were adopted from Kelman *et al*[19] and American Headache Society Consensus statement, respectively[18,19]. They were questioned about their knowledge of diagnostic criteria, prophylactic therapy and migraine triggers. They were also asked to choose appropriate answers from a list of available triggers of migraine and indications and duration for prophylaxis. Distractors were introduced in the triggers and indications of prophylaxis checklists to assess better for recognition (Figures 1 and 2). Migraineurs were further asked questions about their triggers, abortive and prophylactic therapy use and efficacy, medical consultation seeking, and over-the-counter (OTC) drug use. For diagnosis, ICHD-3 diagnostic criteria of migraine with aura, migraine without aura, and chronic migraine were embedded in the questionnaire. Respondents were asked to self-diagnose by matching their symptoms to these criteria within the questionnaire. Migraine cases (migraineurs) were the respondents who chose any type of migraine after going through all the diagnostic criteria. Self-awareness of migraine was defined as migraineurs who thought they had a migraine, while cases who answered "no" or "not sure" when

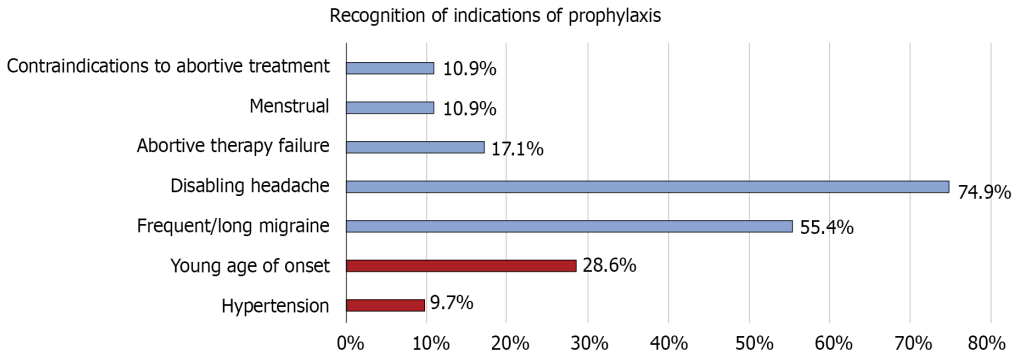

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Figure 1 Knowledge of indications of migraine prophylaxis in physicians. The answers highlighted in red indicates distractors which were not true indications of prophylaxis and added as distractor for more accuracy and to lower bias.

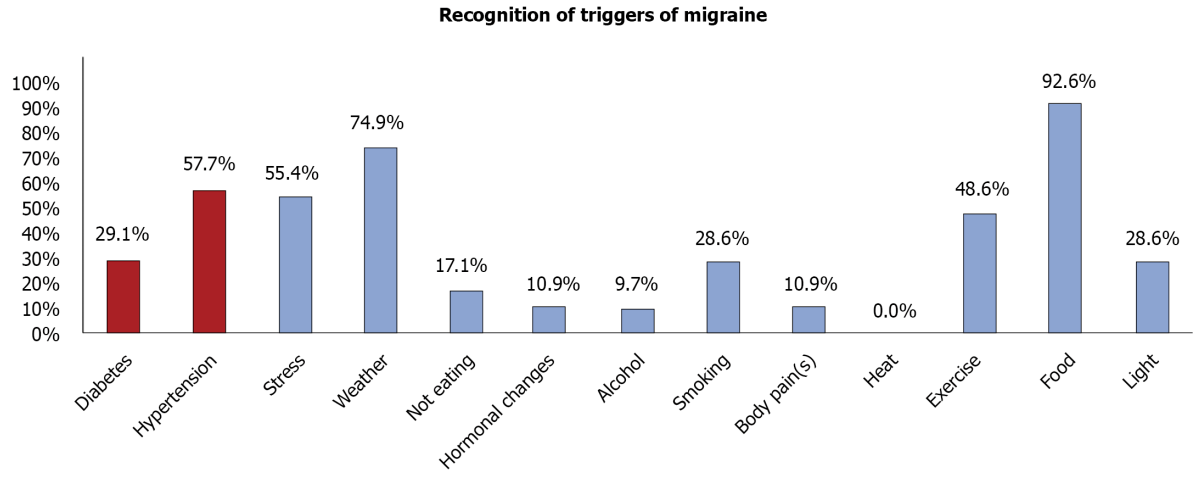

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Figure 2 Knowledge of triggers of migraine in physicians. The answers highlighted in red indicate distractors which were not true triggers of migraine and were added as distractor for more accuracy and to lower bias.

asked if they had migraine were termed unaware. Sample size and sampling: a migraine prevalence of 30% in physicians was assumed (greater than the general population migraine prevalence of 22.5% in Pakistan) and sample size for a prevalence study was calculated for an estimated physician population of 100000 with a confidence interval level and precision of 95% and 6%, respectively. Source Forge's free online sample size calculator was used (sampsize.sourceforge.net). The sample size determined was 186 for the prevalence study.

Statistical analysis and reporting

Reliability testing of migraine awareness was performed with the correlation coefficient (κ) to assess agreement between those who thought they had a migraine (self-aware) and confirmed cases of migraine. The sensitivity and specificity of the self-awareness of migraine were calculated by comparing it with the final diagnosis. The prevalence of migraine was calculated among all the respondents, including the excluded ones, to assess the actual prevalence of the disease in the physician and medical student population. Data analysis was run between groups using R version 1.4.1106, with an additional package of epitools. Chi-square, Mann–Whitney and Fisher's exact tests were applied wherever applicable after tests of the normalcy of distribution (Shapiro–Wilk). Graphs, tables and figures were made using Microsoft Office 2016 and Microsoft Visio. This study was reported in accordance with The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines[20].

RESULTS

Participant characteristics

We distributed the questionnaire to a total of 275 subjects and managed to get a response from 213 of them, setting our response rate at 77.5%. One hundred and ninety participants fulfilled the inclusion criteria. After the application of exclusion criteria, we were left with 175 participants. Among them, 39 were medical students, and the rest of them were physicians. Males and females were symmetrically represented, with 88 males and 87 females. The average age was 25.7 ± 4.1 years. Most of our subjects (56%, n = 98) belonged to the specialty of medicine and allied, 30% (n = 51) to surgery and allied, and 5% (n = 9) to others (including pathology, radiology, *etc.*). A majority (62.3%, n = 109) of our respondents never consulted anyone for the headaches. The basic characteristics and demographic data of participants are summarized in Table 1.

Prevalence of migraine

Forty-eight (27.4%) of our 175 respondents were diagnosed with migraine using the questionnaire-embedded, self-diagnosis algorithm. This made the total prevalence of migraine in our sample of physicians and medical students 24.4%. Females, as expected, had higher prevalence (n = 28, 32.2%) compared to males (n = 20, 22.7%) among the final sample.

Awareness of migraine

Only 21 (43.8%) of our 48 migraineurs were fully aware of their disease before the application of the embedded criteria, while eight (16.7%) and 19 (39.6%) were completely unaware and not sure, respectively. Similarly, out of 127 non-migraineurs, 126 correctly thought they did not have a migraine. This made the sensitivity and specificity of this self-awareness 43.8% and 99.2%, respectively. The correlation coefficient Cohen's between self-awareness and migraine diagnosis was 0.52, showing a moderate level of association. The physicians' diagnosis of migraine had similar sensitivity (37.5%), specificity (97.6%), and correlation coefficient values (0.43).

Knowledge of migraine

A major proportion of participants (36.7%) erroneously believed that having any type of aura is essential for diagnosing migraine (Figure 3). Almost half of the respondents (n = 85, 48.6%) said they did not remember the diagnostic criteria of migraine, while 13% had never heard about the criteria at all. 11.4% of respondents did not know that prophylactic therapy even existed, while only 33.7% said they remember prophylaxis indications. Only 13.7% (n = 24) could correctly identify the correct duration of prophylaxis while 57.1% (n = 100) of subjects did not know, 21.1% (n = 37) underestimated, and 8% (n = 14) overestimated the duration of prophylactic therapy of migraine. Respondents were able to recognize, on average, just 1.3 of 5 real indications and 3.5 of 11 real triggers. Stress was by far the most commonly recognized trigger, recognized by 92.6% of respondents.

Consulters versus non-consulters

Only 60.6% (n = 66) respondents had sought consult. In general, consultation seekers had better knowledge of diagnostic criteria and prophylactic therapy in the subjective questions. The difference almost reached significance in the knowledge about prophylactic therapy (Table 2), where 57.8% of consulters said they remembered the indications of prophylaxis compared with just 28% of non-consulters (OR: 1.84, P = 0.05). Similarly, only 40.4% of those who chose not to consult correctly believed that aura is essential for a migraine diagnosis compared with a majority (59.1%) of consultation seekers (OR: 0.47, P = 0.02). Paradoxically, non-consulters were more likely to correctly identify the monthly headache rate cut-off for initiation of prophylaxis (30.3%) *versus* consulters (15.1%), and the difference was significant (P = 0.02). However, upon further analysis, it was revealed that consulters were more likely than non-consulters to underestimate the monthly headache rate threshold for starting the prophylaxis, with a mean monthly rate chosen by this group to be 2.85 *versus* 3.18 by the non-consulters (P = 0.03). There was no significant difference in recognizing triggers and indications of prophylaxis between both groups (Table 2). Additionally, headache frequency in both groups was also similar.

Migraineurs versus non-migraineurs

Migraineurs were much more likely to have visited a doctor than non-migraineurs, and the difference was significant (OR: 3.7, P < 0.001). A neurologist consultation was even more significantly associated with a diagnosis of migraine (OR: 17.4, P < 0.001). Females were more likely (31.8%) to have migraines than were males (22.9%), although the difference was not significant. Similarly, there was no significant difference between knowledge of duration or prophylaxis indications and triggers between migraineur and non-migraineur populations.

Migraineurs were more likely than non-migraineurs to remember the diagnostic criteria (52% *vs* 32%, OR: 2.26, P = 0.016). They were also more likely to know prophylaxis indications (43% *vs* 29.9%), but the difference here was just above significance (P = 0.08). Headache attacks per month were significantly higher in migraineurs (median 2 ± 4) than non-migraineurs (0.5 ± 2 IQR), and the difference was

Table 1 General characteristics and responses of all subjects

Characteristics	Results (*N* = 175), *n* (%)
Gender	Females: 88 (50.3)
	Males: 87 (49.7)
Age (yr)	Mean: 25.7 ± 4.1
Grade	Medical student: 39 (22.3)
	House officers: 74 (42.3)
	Non-trainee medical officers: 17 (9.7)
	Trainee medical officer: 38 (21.7)
	Senior registrar: 4 (2.3)
	Assist professor: 2 (1.1)
	Professor: 1 (0.6)
Specialty of doctors	Medicine & allied: 98 (56)
	Surgery & allied: 51 (29.1)
	Others: 9 (5.1)
	Not answered: 17 (9.7)
Do you have migraine?	Yes: 22 (12.6)
	No: 109 (62.3)
	Maybe: 44 (25.1)
Confirmed migraine after reading the ICHD-3 criteria of all 3 types of migraine	Migraine without aura: 36 (20.6)
	Migraine with aura: 9 (5.1)
	Chronic migraine: 3 (1.7)
	No migraine: 127 (72.6)
Consulted any physician	GP: 19 (10.8)
	Medical specialist: 22 (12.6)
	Neurologist: 10 (5.7)
	Ophthalmologist: 19 (10.8)
	Other: 9 (5.1)
	No consultation: 110 (62.8)
Physician able to diagnose migraine	Yes: 45 (25.7)
	No: 9 (5.1)
	Maybe: 9 (5.1)
	Never consulted: 112 (64)
Knowledge of diagnostic criteria of migraine	Heard and remember it: 66 (37.7)
	Heard about it but don't remember: 85 (48.6)
	Never heard about it: 24 (13.7)
Knowledge of prophylaxis of migraine	I know its indications: 59 (33.7)
	I knew its indications but don't remember: 70 (40)
	Know only that it exists: 26 (14.8)
	Don't know about it at all: 20 (11.4)
Aura is essential for migraine?	Yes: 66 (37.7)
	No: 83 (46.8)
	Not sure: 26 (14.7)

Duration of standard prophylactic therapy of migraine?	Do not know: 100 (57.1)
	1 mo: 10 (5.7)
	3 mo: 27 (15.4)
	6 mo[1]: 24 (13.7)
	12 mo: 14 (8)
Monthly headache rate for prophylaxis	≥ 2 per mo: 64 (36.6)
	≥ 3 per mo: 52 (29.7)
	≥ 4 per mo[1]: 43 (24.6)
	≥ 5 per mo: 15 (8.6)
	Not available: 1 (0.6)
Used abortive (migraine patients only)	Yes: 12 (25)
	No: 34 (70.8)
	Maybe: 2 (4.2)
Used prophylactic therapy (migraine patients only)	Yes: 9 (18.7)
	No: 38 (79.2)
	Not sure: 1 (2.1)

[1]Chosen as the standard in accordance with American Headache Society (AHS) guidelines.

significant ($P < 0.01$).

Aware versus unaware migraineurs

Awareness of one's own disease was more common in females (53%) than in males (40%), but the difference was not significant. Migraine-aware respondents were significantly more likely to have visited a physician (81%) than were unaware migraineurs (44%, OR: 5.0, $P = 0.01$). Neurologist consultation, in particular, was more common in migraine aware (6/21) *versus* unaware (2/27, OR: 9.6, $P = 0.024$) participants. All knowledge questions related to diagnosis and prophylaxis had similar results in both groups (Table 3).

DISCUSSION

Our study presents the first extensive data on awareness and knowledge of migraine among physicians in Pakistan, with a point-prevalence of migraine at 24.4%. A similar prevalence has been reported in neighboring countries in the region[21,22]. Herekar *et al*[12] have previously reported a 1-year prevalence of migraine in the general population of Pakistan to be 22.5%. The differences in prevalence have been attributed to methodological variations and changes in cultural attitudes towards disease that lead to underdiagnosis in certain subsets of the population[23,24].

Lack of awareness and knowledge of migraine and its management among physicians causes a striking yet avoidable burden on its demographics. One of the critical reasons for underdiagnoses of migraine is unfamiliarity with the diagnostic criteria and the reluctance to use diagnostic tools among physicians[5,25]. Kristoffersen *et al*[16], who surveyed knowledge of Neurology residents in Norway regarding migraine, reported lapses in the knowledge of neurology residents below the bare minimum. Only half of the neurology residents had used the diagnostic criteria regularly, undoubtedly leading to inadequate familiarity with migraine presentations and subsequent underdiagnosis. Gültekin *et al*[5] reported that only 10% of primary care physicians in Turkey could give the complete diagnostic criteria of migraine. We report similar findings in our population, as 62% of participants in our study admitted not remembering the diagnostic criteria. When tested objectively, 38% believed in the myth that migraine could not be diagnosed without aura. This further indicates a fundamental unfamiliarity with types of migraine, migraine without aura in particular. The inadequate familiarity with not only the diagnostic criteria but the types of migraine as well can undeniably lead to an underdiagnosis and mismanagement of a plethora of cases.

The migraine triggers originated from self-reports by patients, but some have been experimentally verified[26]. Advice regarding triggers has varied through the years. Historically, it was argued that the best way to avoid headache was to avoid the triggers. Still, recent evidence suggests that the association of triggers with the headache is a learned process of the brain that subsequently attaches it to the

Table 2 Results of analysis between groups based on consult-seeking behaviors and migraine diagnoses

	Consultation seeking			Migraine		
	Non-consulters (*n* = 109)	**Consulters (*n* = 66)**	***P***	**Migraineurs (*n* = 48)**	**Non-migraineurs (*n* = 127)**	***P***
Gender	Females: 54 (49.5%); Males: 55 (50.5%)	Females: 34 (51.5%); Males: 32 (48.5%)	0.8	Females: 28 (58.3%); Males: 20 (41.7%)	Females: 60 (47.2%); Males: 67 (52.7%)	0.19
Knowledge of diagnostic criteria	Remember: 37 (33.9%); Don't remember:72 (66.1%)	Remember: 29 (43.9%); Don't remember: 37 (56.1%)	0.24	Remember: 25 (52.1%); Don't remember: 23 (47.9%)	Remember: 41 (32.3%); Don't remember: 86 (67.7%)	**0.016;** OR: 2.26 (95% CI: 1.1-4.5)
Know prophylaxis indications	Yes: 31 (28.4%); No:78 (71.6%)	Yes: 38 (34.9%); No: 28 (42.4%)	0.05	Yes: 21 (43.7%); No: 27 (56.2%)	Yes: 38 (29.9%); No: 89 (70.1%)	0.08
Aura essential for diagnosis?	Yes: 65 (59.6%); No or not sure: 44(40.4%)[1]	Yes: 27 (40.9%); No or not sure: 39 (51.1%)[1]	**0.016;** OR: 0.47 (95%CI: 0.25-0.87)	Yes: 22 (45.8%); No or not sure: 26 (54.2%)	Yes: 70 (55.1%); No or not Sure: 57 (44.9%)	0.27
Consulted		Neurologist: 10 (15.2%); Other doctor(s): 56 (84.8%); None: 0 (0%)		Neurologist:8 (16.7%); Other doctors:21 (43.7%); None: 19 (39.6%)	Neurologist: 2 (1.6%); Other doctors: 35 (27.6%); None: 90 (70.9%)	**< 0.001**
Monthly attack cutoff for prophylaxis[2]	Correctly Identified: 33 (30.3%); Could not Identify: 75 (68.8%)	Correctly Identified: 10 (15.1%); Could not Identify: 56 (84.9%)	0.02	Correctly Identified: 16; Could not Identify: 32	Correctly Identified: 27 (21.4%); Could not Identify: 99 (78.6%)	0.11
Know correct duration of prophylaxis?[3]	Yes: 28 (25.7%); No: 81 (74.3%)	Yes :20 (30.3%); No: 46 (69.7%)	0.5	Yes: 13 (27%); No: 35 (73%)	Yes: 35 (27.5%); No: 92 (72.5%)	0.94
Frequency of headache attacks (per month)	None: 31 (28.4%); ≤ 1: 39(35.8%); 2: 17 (15.6%); 3: 6 (5.5%); ≥ 4: 16 (14.7%)	None: 13 (19.7%); ≤ 1: 22 (33.3%); 2: 13 (19.7%); 3: 8 (12.1%); ≥ 4: 10 (15.1%)	0.4	None: 4 (8.3%); ≤ 1: 16 (33.3%); 2: 9 (18.7%); 3: 6 (12.5%); ≥ 4: 13 (27.1%)	None: 40 (31.5%); ≤ 1: 45 (35.4%); 2: 21 (15.7%); 3: 8 (6.3%); ≥ 4: 13 (2.4%)[1]	**< 0.01**
Total triggers recognized	Median: 4, IQR: 5	Median: 3, IQR: 4	0.29	Median: 3.5, IQR: 3	Median: 4, IQR: 5	0.297
Total indications recognized	Median: 2, IQR: 1	Median: 1, IQR: 1	0.21	Median: 1, IQR: 1	Median: 1, IQR: 1	0.22
Distractor(s) recognized as triggers	Yes: 47 (43.1%); No: 62 (56.9%)	Yes: 29 (43.9%); No: 37 (56.1%)	0.91	Yes: 22 (45.8%); No: 26 (54.2%)	Yes: 54 (42.5%); No: 73 (57.5%)	0.69
Distractor(s) recognized as Indications	Yes: 37 (33.9%); No: 71 (65.1%)	Yes: 17 (25.7%); No: 49 (74.2%)	0.23	Yes: 16 (33.3%); No: 32 (66.7%)	Yes: 38 (22.1%); No: 88 (87.9%)	0.68
Migraineurs	Migraineurs: 19 (17.4%); Non-migraineurs: 90 (82.5%)[1]	Migraineurs: 29 (43.9%); Non-migraineurs: 37 (56.1%)[1]	< 0.001; OR: 3.7 (95%CI: 1.8-7.5)			

[1]Indicates statistically significant results.

[2]Monthly headache rate ≥ 4 was chosen as standard for initiation of prophylaxis according to American Headache Society (AHS) guidelines.

[3]A 6-mo duration of prophylaxis was chosen as standard according to AHS guidelines.

IQR: Inter-quartile range; OR: Odd's ratio; CI: Confidence interval.

headache. According to this theory, slow desensitization techniques rather than avoidance strategy is the way forward[27]. Nonetheless, knowledge of the trigger itself is vital for physicians if they counsel the patient appropriately for either strategy. The fact that an average physician in our study could not recognize even half of the triggers from the list points to an apparent deficiency in this knowledge.

Table 3 Subgroup analysis among migraineurs based on awareness of their disease

	Migraine awareness		
	Migraine aware (*n* = 21)	**Not aware (*n* = 27)**	***P***
Gender	Females: 13 (61.9%); Males: 8 (38.1%)	Females: 15 (55.5%); Males: 12 (45.5%)	0.65
Diagnostic criteria	Remember: 12 (57.1%); don't remember: 9 (42.9%)	Remember: 13 (48%); don't remember: 14 (52%)	0.53
Know prophylaxis indications	Know indications: 11 (52.4%); do not know about either prophylaxis or its indications: 10 (47.6%)	Know indications: 10 (37%); do not know about either prophylaxis or its indications: 17 (63%)	0.44
Aura essential for diagnosis?	No: 13 (61.9%); yes or not sure: 8	No: 13 (48.1%); yes or not sure: 14 (51.9%)	0.34
Consulted	Neurologist: 6 (28.6%); Any other physician: 11 (52.4%); Didn't consult: 4 (19%)[1]	Neurologist: 2 (7.4%); Any other physician: 10 (37%); Didn't consult: 15[1] (55.6%)	**0.02;** OR: 9.6 (95%CI: 1.5-96)
Monthly attack cutoff for prophylaxis	Correctly identified: 5 (23.8%); Couldn't identify: 16 (76.2%)	Correctly identified: 11 (40.7%); Couldn't identify: 16 (59.2%)	0.22
Know duration of prophylaxis	Correctly identified: 6 (28.5%); Couldn't identify:15 (71.4%)	Correctly identified: =7 (33.3%); Couldn't identify: 20 (66.7%)	0.83
Respondent's frequency of attacks (per month)	None: 1 (4.8%); ≤ 1: 8 (38.1%); 2: 2 (9.5%); 3: 3 (14.3%); ≥ 4: 7 (33.3%)	None: 3 (11.1%); ≤ 1: 8 (29.6%); 2: 7 (25.9%); 3: 3 (11.1%); ≥ 4: 6 (22.2%)	0.5
Average no of triggers recognized	Median: 3, IQR: 3	Median: 4, IQR: 3	0.32
Average no of indications recognized	Median: 1, IQR: 1	Median: 2, IQR: 1	0.17

[1]Indicates statistically significant results.
IQR: Inter-quartile range; OR: Odd's ratio; CI: Confidence interval.

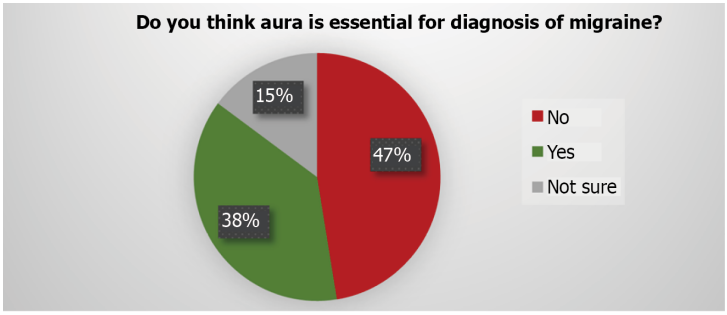

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Figure 3 Belief in the myth that aura is an integral part of migraine diagnosis.

Moreover, perhaps even more worryingly, almost half of the participants chose the distractors (hypertension and diabetes) as triggers.

Menstrual migraine is associated with particularly significant morbidity due to the longer duration, increased severity, and periodicity, and also because of its refractoriness to abortive treatment[28]. The disability associated with it deserves a special mention because it, arguably, is the most common migraine trigger, with 70% of female migraineurs reporting this trigger[28]. It is also one of the most common disabling conditions presented in gynecological practices[29] but 42% of our respondents did not recognize it as a trigger. In comparison, an overwhelming majority (90%) did not know that menstrual migraine can itself be an indication for initiation of prophylaxis, which reveals a vital missing piece in physicians' knowledge on the subject.

Studies on migraine have consistently demonstrated the role of preventive therapy in reducing disease burden[30]. Preventive therapy is central in managing migraineurs with severe and frequent attacks as the overutilization of abortive therapy may frequently lead to medication-overuse headaches or resistant migraine[31]. Preventive therapy is also required in some cases to augment responsiveness to abortive therapy as it reduces the frequency and duration of the migraine attacks and the severity [13]. Silberstein and colleagues demonstrated that preventive therapy (when indicated) combined with abortive was much more effective in reducing the migraine load than abortive therapy alone[31]. Moreover, management of chronic migraine requires an approach involving a combination of abortive, preventive, and behavioral therapy. In our sample, chronic migraine (frequent attacks) as an indication

of prophylaxis was recognized by 50% of respondents, which fares relatively better than recognition of other indications but is still inadequate. On the contrary, only 33% of physicians and medical students thought they remembered the indications of prophylaxis. When tested from a list of indications, a physician could identify only about one indication out of five. These results reveal another vital knowledge gap that needs priority focus.

Physicians, in general, underestimate the role of preventive therapy[31-34]. The American Migraine Communication study highlighted physicians under-rating the disability caused by migraine and thus the need for prophylactic therapy[35]. In contrast, there is some evidence that neurologists, compared with other physicians, tend to emphasize the role of prophylaxis[36]. Physicians' unfamiliarity with preventive therapy means an inability to manage chronic migraine cases properly. Preventive therapy use among physicians in our sample (18%) was similar to the prevalence reported elsewhere in the literature[31,37]. The fact that more than two thirds of physicians in our sample did not remember the indications of prophylaxis when asked subjectively is particularly troubling for a large subset of special cases. These comprise but are not limited to chronic migraine, menstrual-related, resistant migraine, and other more severe forms of migraine, which are contingent upon preventive therapy and are perhaps responsible for several mishandled cases. Additionally, we found no meaningful differences between consulters and non-consulters for recognition of prophylaxis indications. Our inference is that the under-emphasis on preventive therapy in the form of avoidance of triggers or drug therapy is so pervasive that even after consulting a physician for the headache, respondents did not gain any meaningful knowledge of these aspects of the migraine.

Weber *et al*[38] reported that primary care physicians suffering from migraine described receiving more migraine patients in their practice than their healthy colleagues. Their patients were more likely to have a better quality of life. This is perhaps related to the sensitivity of such physicians towards migraineurs. A similar inference can be made from our results, as migraineurs were more likely to state that they knew the diagnostic criteria. However, the difference was not significant when asked the question regarding diagnosis objectively, *i.e.*, the question related to the aura. The improved knowledge of the disease's diagnosis and management in physicians with migraine (Table 2) puts them in a better position to understand and help the patients. Migraineurs in our study were also more likely to have visited a doctor (61.4% *vs* 29.1%). The association was strongest with a neurologist's consultation (OR: 17.4, $P < 0.001$). This potentially represents the role of a consultation, especially with a neurologist, in diagnosing migraine[39]. The subjective feeling of knowledge related to diagnostic criteria as well as prophylactic therapy was also significantly better in consultation seekers (Table 2). We think this is a result of discussion about the disease with their consulting physicians or more intrigue and reflection about the disease resulting from the consultation. The consulting process, the resultant introspection, and perhaps reading about their condition helped physicians improve their knowledge. This is also reflective of the power and efficacy of a medical consultation[39]. The contradictory results on the monthly headache rate threshold of preventive therapy can be logically explained with a further breakdown of data, as consulters favored the prophylaxis more and underestimated the threshold for initiation of prophylaxis, constituting a better trend overall.

Radtke *et al*[25] reported 70% awareness of migraine in their sample in 2012, with a coefficient of agreement value of 0.46 between ICHD-II criteria and awareness. At 44%, migraine in our sample was lower (= 0.52). The sensitivity of physicians' diagnosis among the sample collected by Radtke *et al*[25] was also better at 63%. We did not specify the temporal order of events in our question, *i.e.*, whether they knew about their migraine before consulting a doctor or suspected one after their visit. Hence, this self-awareness of migraine is not mutually exclusive to the consulting physician's diagnosis of migraine in our cases. However, our data hint toward the role of physicians' consultation in producing this self-awareness. Although consulting with physicians could not contribute to better knowledge of the subjects, it still helped diagnose the disease in many cases. The precision of diagnosis was better when consultations came from neurologists (Table 3). However, the number in our sample was too small, and more studies are needed for a more generalizable inference. Our study thus reinforces the earlier findings that the advice to seek consultation for a headache instead of OTC medication use is essential and needs to be practiced by our physicians[39].

The ever-increasing global burden of non-communicable diseases concerning morbidity and the fact that migraine is jumping the ladder of the most prevalent diseases exponentially is alarming[40]. Every effort has to be made for an accurate and timely diagnosis of migraine. Fortunately, with the advent of new data on drug therapy in migraine, this era is also witnessing a remarkable change in its management[41]. Recent studies have shown mechanism-based therapies like anti-calcitonin gene-related peptide monoclonal antibodies (erenumab, tinezumab, fremanezumab and galcanezumabas) as promising drugs in the preventive management of migraine[13,42]. In addition to rapid onset, these drugs also carry fewer adverse effects (mainly injection site reactions). Erenumab specifically has shown effectiveness in a 50% reduction in migraine days, with a favorable safety profile[43]. However, currently, high costs and limited availability of these monoclonal antibodies are a challenge in migraine management on a global level. Various methods can be applied to improve awareness and knowledge of migraine among the physicians who serve as the first encounter with health care for patients with headaches. We suggest that the interventions for improvement have to be incorporated early in the course of a physician's clinical life. One such strategy can be dedicated lectures on migraine in medical

schools, focusing on it as a high-yield topic of examination, including standardized patients with migraine in clinical exams. New graduates should be educated by headache specialists on migraine diagnosis and management before starting internships. For practicing physicians, the interventions can include yearly workshops, continuing medical education activities, and the provision of migraine diagnostic and management posters to be placed in the clinics. Virtual education, which saw its role vastly inflated during the current coronavirus disease-2019 pandemic, can be utilized to maximize education on migraine among physicians. It is also imperative to prospectively study the effects of increased awareness of migraine among physicians to establish the amplitude of change it may carry in decreasing the global burden of disability with regard to migraine. Together with the introduction of more effective preventive and possibly curative treatments, this may also play a key role in reducing the global prevalence of migraine.

Our study had some limitations grounded in the study design used. Firstly, the subjective questions on diagnostic criteria and prophylactic treatment were subject to social desirability bias as most respondents were not open to accepting their knowledge deficit. Secondly, we did not use any migraine diagnosis registry due to lack of the aforementioned, but our data collection team ensured that respondents understood the diagnostic criteria during collection. Thirdly, excluding the cases that did not experience headaches may have potentially excluded a specific subset of doctors whose knowledge was not tested. This, albeit small, was a potential source of sampling bias in our study. Fourthly, although almost all the questionnaires were filled in the presence of one of the study team members and we tried to keep the questionnaire as short as possible, there was still a possibility that some of the participants might not have read the questions and criteria thoroughly; an inherent possibility with the questionnaire-based studies. Despite these limitations, we believe the study was largely free from any systematic biases.

CONCLUSION

Despite its high prevalence and high associated morbidity, migraine diagnosis and management knowledge remain below the minimum functionally required among physicians in Pakistan. Steps need to be taken to bridge the knowledge gap among doctors to address underdiagnosis and mismanagement of the disease.

ARTICLE HIGHLIGHTS

Research background

Despite its high prevalence, migraine remains underdiagnosed worldwide. A significant reason is the knowledge gap in physicians regarding diagnostic criteria, clinical features, and other clinical aspects of migraine.

Research motivation

This research was conducted to see whether migraine follows the same trends of underdiagnosis in Physicians of Pakistan as globally.

Research objectives

We aimed to measure the knowledge deficit in physicians and medical students and to assess the prevalence of migraine in the same population.

Research methods

An online questionnaire was developed and distributed among physicians and final-year medical students on duty in various medical and surgical specialties of Allied and DHQ Hospitals, Faisalabad, between October 2018 and October 2019. Inclusion criteria were public practicing physicians who experience headaches, while those who never experienced headaches were excluded. Different questions assessed respondents on their knowledge of triggers, diagnosis, management, and prophylaxis of the migraine headache. They were asked to diagnose themselves using embedded ICHD-3 diagnostic criteria for different types of migraine. Graphs, tables and figures were made using Microsoft Office 2016 and Microsoft Visio, and data analysis was done in R Studio 1.4.

Research results

We had 213 respondents and 175 fulfilled inclusion criteria, with 99 (52%), 58 (30%) and 12 (6.3%) belonging to specialties of medicine, surgery, and others, respectively. Both genders were symmetrically represented (88 male and 87 female). Fifty-two (24.4%) of our 213 respondents were diagnosed with migraine, with 26 (50%) being aware of it. Females had higher prevalence among study participants (n =

28, 32.2%) compared to males (n = 20, 22.7%, P = 0.19). A majority (62%) of subjects never consulted any physician for their headache. Similarly, a majority (62%) either never heard or did not remember the diagnostic criteria of migraine, and 38% falsely believed that having any type of aura was essential for diagnosing migraine. The consultation rate was 37% (n = 65), and migraineurs were significantly more likely to have consulted a physician, a neurologist in particular (P < 0.001). Consulters and migraineurs fared better in the knowledge of diagnostic aspects of the disease than their counterparts. There was no significant difference in other knowledge aspects between consulters and non-consulters and migraineurs and non-migraineurs.

Research conclusions

Critical knowledge gaps exist between physicians and medical students, potentially contributing to the misdiagnosis and mismanagement of migraine cases.

Research perspectives

Migraine remains an underdiagnosed disease in the general population as well as among healthcare providers. Education, timely diagnosis, and management will help reduce its global burden.

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FOOTNOTES

Author contributions: Choudry H, Ata F and Naveed Alam M were responsible for study design; Choudry H, Ata F, Naveed Alam M, Ruqaiya R and Qaiser Ikram M did the questionnaire design; Choudry H and Naveed Alam M analyzed the data; Choudry H and Ata F were responsible for the manuscript revision; all authors participated in data collection and manuscript writing.

Institutional review board statement: The study was conducted following the guidelines of the Declaration of Helsinki and approved by the institutional ethical review committee of the Faisalabad Medical University (No. 000319). The ethics committee waived informed consent.

Informed consent statement: Informed consent from patients was waived by the ethics committee.

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

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STROBE statement: The authors have read the STROBE checklist of items, and the manuscript was prepared and revised according to the STROBE checklist of items.

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SYSTEMATIC REVIEWS

Role of the circulatory interleukin-6 in the pathogenesis of gliomas: A systematic review

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Abstract

BACKGROUND

Glioma is the most common primary tumor in the brain originating from glial cells. In spite of extensive research, the overall survival rate is not enhanced. A number of published articles observed differentially circulating levels of cytokines in glioma. Interleukin-6 (IL-6) protein coded by IL-6 gene is regulated by the immune system and it has been found to have a significant role in progression and apoptosis resistance of glioma.

AIM

To review the role of circulatory IL-6 in the development and progression of glioma and its utility as a biomarker.

METHODS

Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines were applied to filter the relevant studies based on inclusion and exclusion criteria. We used a combination of keywords and the *Reference Citation Analysis* (*RCA*) tool to search the potential studies and performed data extraction from selected studies.

RESULTS

The published results were inconsistent; however, most studies showed a significantly higher IL-6 level in glioma cases as compared to controls. Comparative IL-6 level among the different grades of glioma showed a higher level with low-grade gliomas and lower level with high-grade gliomas.

CONCLUSION

IL-6 level significantly differed between cases and controls, and among different cancer stages, which shows its potential as a diagnostic and prognostic marker.

Key Words: Gliomas; Interleukin-6; Circulatory markers; Diagnostic marker; Prognostic marker

Core Tip: In spite of extensive research in the field of brain oncology, the overall survival is not much improved. There is an urgent need to explore the circulatory markers for diagnosis and prognosis. This systematic review focused on the role of interleukin-6 in brain cancer development and progression and its utility as a diagnostic or prognostic biomarker.

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INTRODUCTION

Gliomas are the most common primary brain tumors in adults, accounting for 80% of malignant brain tumors originating from glial cells[1]. Globally, gliomas show a wide variation in incidence, and it is 0.01–12.7 in males and 0.01–10.7 in females per 100 000 people[2]. The lowest incidence is in Africa and highest in Northern Europe[2]. Gliomas are an increasing cause of death in children and the third most common in adolescents and adults[2]. According to the World Health Organization (WHO) classification, the most common occurring histological grade of gliomas is astrocytic tumors (grades I–III) and oligodendroglial tumors (grades II–III), ependymoma (grades I–III) and glioblastoma (grade IV)[3,4]. Glioblastoma is aggressive in nature and the survival rate is low, with death within 2 years of diagnosis despite receiving maximal surgical removal of the tumor and medical therapies including chemotherapy and radiotherapy. Therefore, there is an urgent need to find comprehensive treatment strategies to enhance the survival rate[5].

Adapting the Virchow theory, various studies concluded that inflammation is one of the major hallmarks of cancer formation[6,7]. Within the cancerous microenvironment, inflammatory cells and cytokines have pleomorphic roles. On the one hand, these aid in tumor suppression, while on the other hand, they support malignant cell transformation, tumor growth, inhibition of apoptosis, invasion, angiogenesis, cell migration, tumor cells differentiation and immuno-suppression[8-11]. A number of studies showed varied circulating levels of cytokines in glioma. On the basis of The Cancer Genome Atlas database, interleukin (IL)-6 has a significant role in progression and apoptosis resistance of glioma [12-15].

IL-6 is a pleiotropic proinflammatory cytokine with a 21–28-kDa four-helix bundled glycoprotein with 184 amino acids[16,17]. Under normal conditions, IL-6 secretion is initiated in response to stimuli such as viruses, UV and secretion of other cytokines, and it is released by a variety of cells including macrophages, monocytes, hematopoietic cells, stromal cells, muscles cells and epithelial cells. IL-6 has a significant role in the process of immunity, inflammation, angiogenesis, neural development, reproduction, metabolism hematopoiesis, and bone remodeling[18,19]. In tumor vasculature, IL-6 is released by tumor cells, tumor-infiltrating immune cells and fibroblast stromal cells, and induced by several factors such as prostaglandin E2, IL-1β, hypoxia, nuclear factor (NF)-κB, miRNAs and lack of signal transducer and activator of transcription (STAT)3 inhibitors[16,18,20-23]. IL-6 exerts its function by binding to its receptor either by membrane bound receptor (mIL-6R), the classical pathway or by soluble receptor (sIL-6R), the trans-signaling pathway. Binding of IL-6 to its receptor causes the activation of gp130, which subsequently activates cytoplasmic tyrosine kinases (Janus kinase, JAK) *via* its phosphorylation that is responsible for intracellular signaling by phosphorylation of STATs (especially the STAT3 pathway). Phosphorylated STAT3 dimer translocates to the nucleus, which leads to the transcription of targeted genes (*Bcl-2, Bcl-xL, Cyclin D1, VEGF, etc.*) and production of other proinflammatory cytokines and exerts an acute-phase response[16,18,24]. These activated genes may code for the proteins involved in cell survival (cyclin D1, survivin and MYC)[18], antiapoptotic condition (Bcl-x and MYC)[16,25], angiogenesis (vascular endothelial growth factor; VEGF)[16], invasion (MMP)[16], tumor growth and immunosuppressive factor secretion [transforming growth factor (TGF)-β, IL-10 and VEGF][26,27]. A systematic diagram showing the physiology of IL-6 is shown in Figure 1. The STAT3 signaling pathway is downregulated in different ways, such as suppressor of cytokine signaling (SOCS)3 inhibits phosphorylation of JAK proteins and protein inhibitor of activated STAT3 (PIAS3) inhibits dimerization of STAT3 monomers.

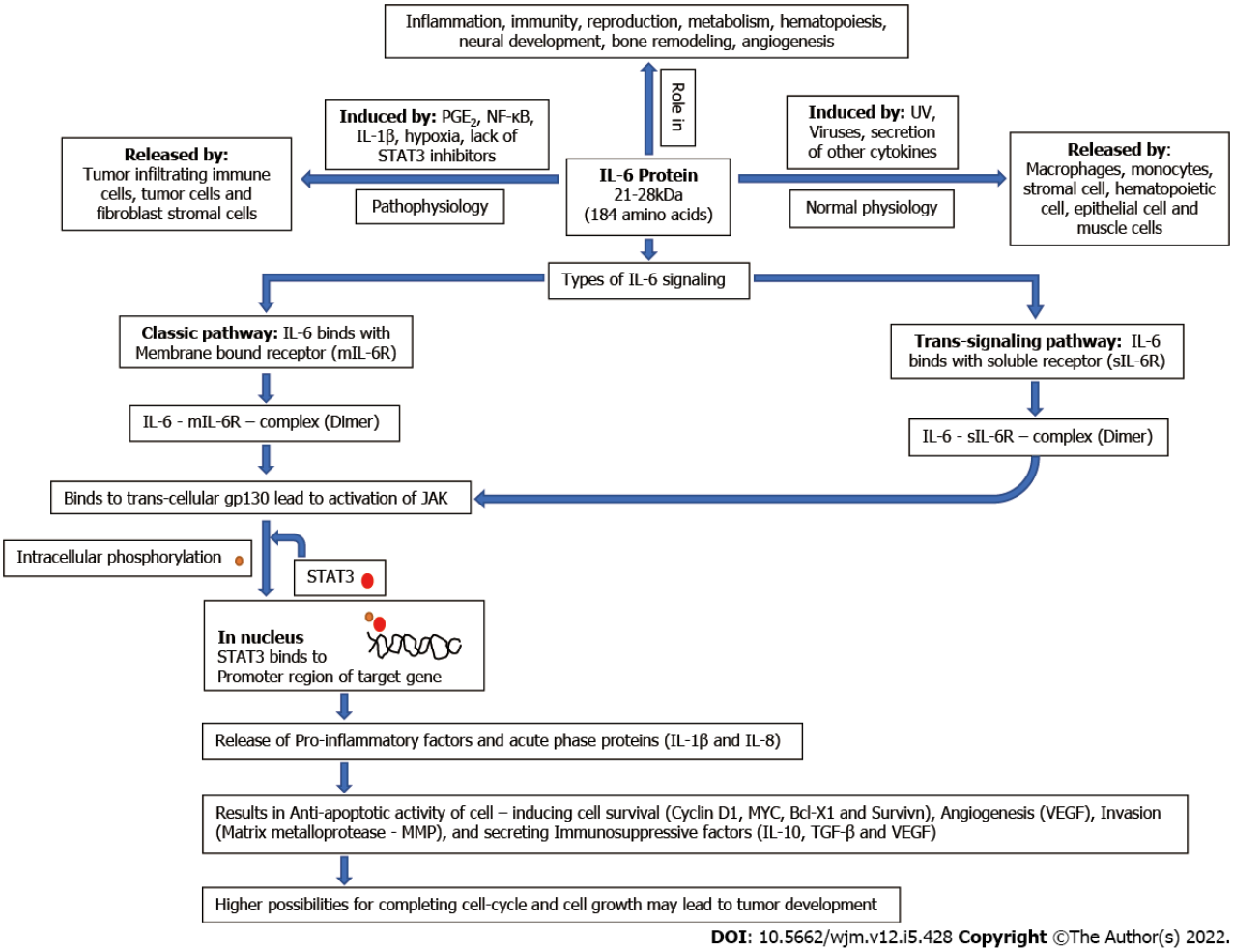

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Figure 1 Physiology of interleukin (IL)-6. IL-6 has regulatory role in various physiological processes such as inflammation, immunity and reproduction. IL-6 is induced by viruses and UV, *etc.*, and is released by macrophages, monocytes and stromal cells under normal physiological conditions, and under pathophysiological conditions, it is induced by nuclear factor-κB, prostaglandin E2, hypoxia and released by tumor-infiltrating immune cells and tumor cells, *etc.* IL-6 can activate the STAT3 signaling pathway either by the classical pathway or trans-signaling pathway. Activation of STAT3 can upregulate a variety of genes and may have an important role in tumor formation.

Besides these key roles, IL-6 also plays key roles in inflammation, proliferation and differentiation of B and T lymphocytes and natural killer cells[28]. IL-6 blocks MHC class II expression of Th1 cells and halts the secretion of IL-2 and interferon-γ and hence reduces cytotoxic T-lymphocyte activity[29]. Inhibition of the activity of T lymphocytes helps cancer cells to inhibit the immune response. Several miRNAs are involved in the production of IL-6 in a paracrine manner[30]

In various studies, a higher level of IL-6 was found to be associated with tumor progression and poor survival rate in several cancers including glioma. In glioma, IL-6 affects tumor formation and progression by triggering the JAK/STAT3 signaling pathway, which may further lead to continuous cell growth[31], tumor development, cell invasion and migration[32,33], angiogenesis[34] and inhibition of apoptosis[35,36]. The mRNA expression of IL-6 gene has been found to correlate with higher grade of glioma (glioblastoma)[37], in addition IL-6 gene amplification in tissues samples was 54% (15 of 36) on glioblastoma and none of 17 in lower grade of glioma[38]. Immunohistochemistry revealed that IL-6 receptors were totally absent in normal brain tissue and all the tissues of glioblastoma samples[39]. STAT3 promotes tumor growth by inhibiting apoptosis in glioma and increased level of phosphorylated STAT3 is found in recurrent glioblastoma as compared to primary glioma[40].

In this systematic review, we reviewed all the published case–control studies investigating the role of circulatory IL-6 in the development and progression of glioma and its utility as a diagnostic or prognostic biomarker.

MATERIAL AND METHODS

The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analysis) guidelines[41] were adapted to perform this systematic review.

Literature search strategies

An exhausted literature search on March 1, 2021 was done by two research scientists independently using various combination of keywords "glioma", "glioblastoma", "interleukin-6", "IL-6", "case-control study", "ELISA", "enzyme linked immunosorbent assay" "circulatory levels of IL-6" using the Reference Citation Analysis™ (RCA) tool, which is an artificial intelligence technology-based open multidisciplinary citation analysis database. On RCA window, keywords were entered in the designated area and after selecting the "Find an Article", we obtained a list of the latest highlighted articles that was further filtered by selecting Impact Index Per Article. The systematic search was limited to articles published in English language. The relevant full-text articles were obtained. References were also evaluated to retrieve additional studies. The researchers thoroughly evaluated full-length original articles based on the inclusion and exclusion criteria for the inclusion in this systematic review [41].

Inclusion criteria

All the retrieved studies were screened and filtered on the basis of PICO (patient/population, intervention, comparison and outcomes) strategy as follows: (1) Participants: histopathological confirmed cases of glioma; (2) intervention: conditions including progression and invasion of glioma; (3) comparison: controls free from any malignancy; (4) observation: IL-6 expression level by ELISA or multiplex assay; and (5) case–control studies. A flow chart (PRISMA) showing the search strategy is shown in Figure 2.

Exclusion criteria

The studies were excluded based on the following criteria: (1) Studies with insufficient information regarding the level of IL-6; (2) review articles, meta-analyses, editorials, letters, and duplicate articles; (3) conference proceedings; and (4) not in English language.

Data extraction and study characteristics

Gathering of information from the relevant articles was carefully done on the basis of inclusion criteria. From each relevant study, the following information was collected and organized in Table 1: First author's last name, year of publication, ethnicity of the study population, sample size, sample collected (serum or plasma), method of analysis (ELISA), IL-6 expression and glioma outcome (increased or decreased) in comparison to controls.

RESULTS

A total of 953 studies were identified in the literature search and five studies have been included for full evaluation in this systematic review (Figure 2). The critically evaluated studies are summarized in Table 1.

The study of Doroudchi *et al*[42] comprising 38 cases and 26 controls found a significantly decreased level of IL-6 in the serum of glioma cases (2.34 ± 4.35 pg/mL) as compared to controls (4.67 ± 4.35 pg/mL), while some other studies observed a significantly increased level of IL-6 in cases as compared to controls[8,42,43]. A study including 55 cases of glioblastoma and 20 healthy controls found fourfold upregulation of IL-6 in the cases of glioblastoma as compared to controls[8]. In contrast, Schwartzbaum *et al*[44], with a large number of cases of glioma (n = 487) and healthy controls (n = 487), did not find any significant (OR = 0.77) association of case–control correlation in differentially expressed level of IL-6. Level of IL-6 in glioma patients aged > 30 years showed a lower value as compared to young patients; however, the investigators did not find a significant correlation[42].

Comparative level of IL-6 among the different grade of glioma cancer observed a higher level (4.02 ± 7.80 pg/mL) with low grade of cancer and lower levels (1.74 ± 1.55 pg/mL) with high grade of cancer [42]. In contrast, in a few studies, the serum levels of IL-6 increased with the progression of glioma grading[43]. Univariate analysis indicated that the increased level of IL-6 declined after surgical removal of the glioma[43]. This indicates that, along with immune cells including inflammatory cells, tumor cells can also release the IL-6. Zhenjiang *et al*[45] has compared the circulating level of IL-6 along with other cytokines between glioblastoma multiforme (GBM) and non-GBM malignant glioma. They observed a detectable concentration of IL-6 in 45%–50% of cases, along with IL-4 and IL-5 in GBM patients, while 55%–60% cases with non-GBM glioma expressed IL-6 along with IL-4 and IL-5[45]. The investigators also analyzed the combination effects of selected cytokines (IL-4/IL-5/IL-6) on patients' survival and found that if all were present or all absent, it was associated with better survival rate.

DISCUSSION

Many biomarkers are differentially expressed in cases versus controls using tissue samples; however, the current need is based and focused on circulatory biomarkers. Recently, liquid biopsy has been used

Table 1 Characteristics of the selected studies included in this review literature

No.	Author name	Year	Region	Sample	Case (glioma)	Control	IL-6 level (pg/mL)
1	Doroudchi *et al* [42]	2013	Iran	serum	38	26	Decreased as compared to controls
2	Shan *et al*[43]	2015	China	Serum	86	18	IL-6 level increased with the elevation of grade
3	Albulescu *et al*[8]	2013	Romania	Serum	55	20	3-fold upregulated than control
4	Schwartzbaum *et al*[44]	2017	Norway	Serum	487	487	insignificant association with the disease
5	Zhenjiang *et al*[45]	2018	Sweden	Serum	GBM = 145	Non-GBM = 60	45%–50% cases of GBM observed with detectable level of IL-6 & 55%–60% cases of Non-GBM malignant glioma observed with detected level of IL-6

IL-6: Interleukin-6; GBM: Glioblastoma.

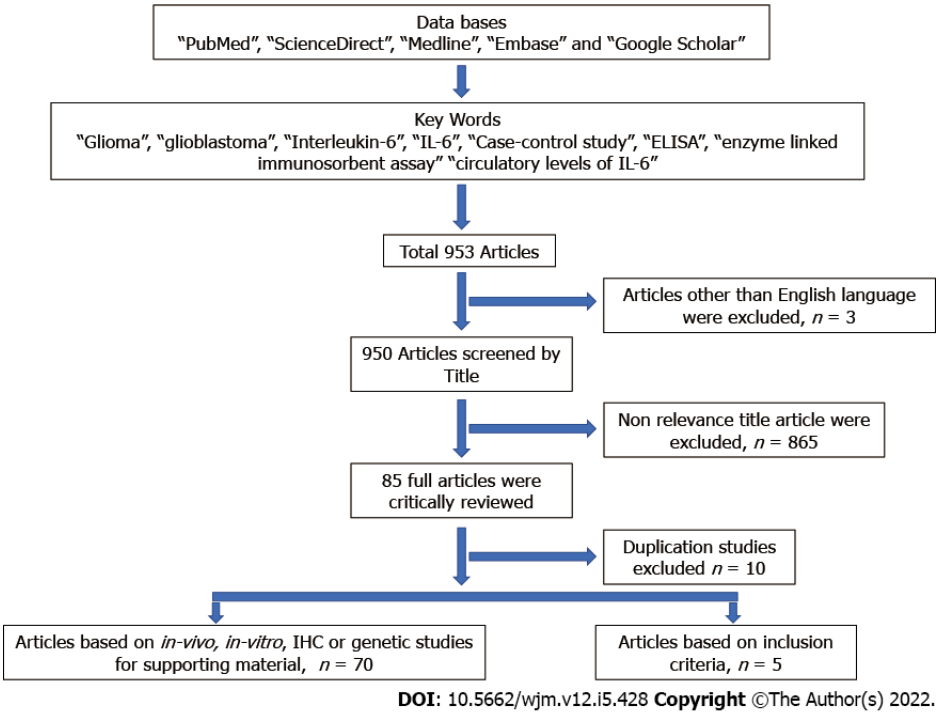

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Figure 2 Electronic search. This review was based on a search of electronic databases using the keywords shown. The resulting 953 articles were screened and assessed by language and three were excluded. The remaining 950 articles were again screened by title and 865 were excluded. The 85 studies were critically reviewed and 10 were duplicates, systematic reviews or meta-analyses and these were excluded. The resultant 75 studies were further divided into two: five studies were included in this mini literature review on the basis of inclusion criteria, and 70 studies based on *in vivo* and/or *in vitro* and/or genetic and/or immunohistochemistry methods were chosen as supporting articles.

to investigate disease development and progression using easily accessible samples like blood or urine or saliva. The published literature shows that there has been a scarcity of studies on the association between human brain cancer and IL-6, and published results are contradictory. However, *in vivo* studies have shown a strong relationship between IL-6 and disease initiation and progression. This indicates an urgent need to design studies to establish how IL-6 can be exploited as diagnostic or prognostic marker.

Glioma is a fatal disease with a reported survival rate of 5% despite surgical resection along with radiotherapy and/or chemotherapy. In spite of extensive research, the overall survival has not much improved[46]. Several experimental studies have shown that IL-6 can be produced by tumor cells, and glioma is characterized by systemic immunosuppression that hinders the response to immunotherapy and helps with tumor progression. Immunotherapy is currently the most explored area of cancer biology and has been shown to increase survival rate in patients with malignancies; however, for glioma its efficacy is currently still being revealed[47]. In glioblastoma, programmed death-ligand 1 (PD-L1) is the critical mediator of immunosuppression and myeloid cells (noncancerous cells) in the tumor microenvironment and circulation express an elevated level of PD-L1[48,49]. Experimental studies have

shown that glioblastoma-derived IL-6 is mandatory and sufficient for the induction of PD-L1, and the correlation between IL-6 and immunosuppression has been recognized *in vitro* and *in vivo*[50,51].

In this systematic review, the overall result was inconclusive. However, we found that most studies observed an elevated level of IL-6 in serum of glioma patients as compared to controls, which indicate the immunosuppressive role of IL-6 in tumor development[3,43]. IL-6, IL-8 and IL-1β are the proinflammatory cytokines and their circulatory expression is upregulated along with downregulated level of anti-inflammatory cytokine IL-4 in glioma, and higher secretion of proinflammatory cytokines is related to the progression of glioblastoma and poor survival rate[8,52,53]. In addition, studies based on expression analysis have shown that expression of IL-6 in glioma cases is significantly different from that in controls. Among grading of glioma, the intensity of IL-6 staining increases with increasing grading, which shows that patients with poorly differentiated tumor have a higher level of IL-6[43]. Therefore, measuring the circulatory levels of IL-6 before and after surgery can be standardized for the prediction of clinical prognosis of glioma.

The uptake and role of IL-6 in glioma invasion has been demonstrated by trans well invasion assay using glioma cell lines (U251 cells, U87 cells T98G cells and A172 cells) incubated with exogenous IL-6 [43]. These studies observed IL-6 in the supernatant of the glioma cell lines[43]. *STAT3* gene is considered to have a conserved sequence and mutation is rare; therefore, it is believed that its constitutive expression is regulated by upstream regulators and IL-6 is one of them[54]. This relationship has been observed in an *in vivo* study that concluded that STAT3 expression is dependent on IL-6 and it is increased in tumor progression[55]; hence, IL-6 has an important role in the development and progression of glioma. Our review found a significant association of IL-6 with disease progression[43, 45] except one study with a lower level of IL-6 in high-grade glioma[42].

The exact regulatory network of IL-6 in the tumor microenvironment is complex; therefore, targeting the underlying mechanism of IL-6 regulation should be undertaken to understand how its upregulation or over-active signaling pathways (especially IL-6/JAK/STAT3 signaling pathway) can help in tumor development, progression or recurrence[56]. Tumor formation is not a consequence of an adverse effect of a single risk factor or cytokine, but rather a group of cytokines, including chemokines, angiogenesis factors and growth factors. Therefore, combinational effects of cytokines can be used to assess their role in glioma and the results may be applied for future tailored immunotherapy and immune-monitoring procedures. Targeting and reducing the molecules hindering the activity of specific therapy may lead to re-sensitization to delivered therapy. Few clinical trials are investigating this idea[57].

CONCLUSION

This systematic review found five published research articles investigating the role of IL-6 as a potential biomarker of glioma in case–controls studies. The overall results are inconsistent; however, most studies found an elevated level of IL-6 in cases of glioma as compared to controls. The level of IL-6 was more than twofold in cases, which means that IL-6 can be considered as potential diagnostic biomarker. In tumors with progressive growth (advanced grade), the circulating level of IL-6 is also increased and hence can be used as a prognostic marker for glioma. Immunotherapy that can produce a durable and tumor-specific immune response can be implemented by disrupting IL-6 signaling and re-sensitizing the immune response to halt or reduce tumor growth and enhance survival rate based on REMARK (reporting recommendation for tumor biomarker prognostics studies) guidelines[58,59].

ARTICLE HIGHLIGHTS

Research background

Interleukin (IL)-6 is a proinflammatory cytokine that is involved in immunity, inflammation, angiogenesis, neural development and reproduction. The tumor microenvironment containing tumor cells, tumor-infiltrating immune cells and fibroblast stromal cells releases IL-6. IL-6 acts on the Janus kinase and signal transducer and activator of transcription factor pathway. These pathways release or associate with proteins that are responsible for major cellular functions.

Research motivation

This systematic review was motivated by a number of research studies that investigated the association between IL-6 and glioma.

Research objectives

In this systematic-review, case-control studies investigating the role of IL-6 with glioma development and progression have been discussed to review the utility of IL-6 as a biomarker.

Research methods
Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines were applied to filter the relevant studies based on inclusion and exclusion criteria. We used a combination of keywords and *Reference Citation Analysis* (*RCA*) tool to search for potential studies and performed data extraction from selected studies.

Research results
Five case–control studies were included for full evaluation. Most studies found a significantly higher level of IL-6 in cases as compared to controls although a study with contradictory results and a study with no difference in IL-6 level was also observed. Il-6 level varies with glioma stage, and some studies have reported lower levels in high-stage of cancer, whereas others have reported higher levels of IL-6 in early-stage glioma. Age at the time of diagnosis of glioma and IL-6 level could also have a significant relationship with glioma.

Research conclusions
IL-6 could be a potential biomarker for the diagnosis and prognosis of glioma as it was increased twofold in cases of glioma as compared to controls.

Research perspectives
Immunotherapy based treatment can be implemented by trigging IL-6 protein associated pathways and re-sensitizing the immune response to inhibit tumor growth and enhance survival rate.

FOOTNOTES

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SYSTEMATIC REVIEWS

Growth differentiation factor 15 as an emerging novel biomarker in SARS-CoV-2 infection

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Abstract

BACKGROUND

Growth differentiation factor (GDF)-15 is a member of a transforming growth factor-β cytokine superfamily that regulates metabolism and is released in response to inflammation, hypoxia and tissue injury. It has evolved as one of the most potent cytokines for predicting the severity of infections and inflammatory conditions, such as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.

AIM

To investigate the utility of GDF-15 in predicting the severity of SARS-CoV-2 infection.

METHODS

PubMed, Reference Citation Analysis, CNKI, and Goggle Scholar were explored by using related MeSH keywords and data such as the first author's name, study duration, type and place of study, sample size and subgroups of participants if any, serum/plasma GDF- 15 level in pg/mL, area under the curve and cut-off value in receiver operating characteristic analysis, method of measurement of GDF-15, and the main conclusion were extracted.

RESULTS

In all studies, the baseline GDF-15 level was elevated in SARS-CoV-2-infected patients, and it was significantly associated with severity, hypoxemia, viral load, and worse clinical consequences. In addition, GDF-15 levels were correlated with C-reactive protein, D-dimer, ferritin and procalcitonin, and it had superior discriminatory ability to detect severity and in-hospital mortality of SARS-CoV-2 infection. Hence, GDF-15 might be used to predict the severity and prognosis of hospitalized patients with SARS-CoV-2.

CONCLUSION
Serial estimation of GDF-15 levels in hospitalized patients with SARS-CoV-2 infection appeared to have useful prognostic value and GDF-15 can be considered a clinically prominent sepsis biomarker for SARS-CoV-2 infection.

Key Words: SARS-CoV-2; Growth differentiation factor 15; Biomarker; Risk-stratification; Prognosis

Core Tip: Growth differentiation factor (GDF)-15 levels are higher in hospitalized patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, and higher levels are associated with disease severity, viremia and hypoxemia. The consistent increase in the concentration of GDF-15 during a hospital stay is associated with worse outcomes. Hence, serial monitoring of GDF-15 concentrations may provide useful prognostic value for hospitalized patients with SARS-CoV-2. GDF-15 appears to be involved in the underlying pathophysiology, laying the foundation for a novel therapeutic approach for SARS-CoV-2.

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INTRODUCTION

Coronavirus disease-2019 (COVID-19), an extremely contagious disease, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is a global public health problem. The index case of this viral infection was confirmed in Wuhan, the capital city of Hubei Province, China in December 2019[1]. Then, SARS-CoV-2 quickly disseminated across the globe, infecting around 430257564 individuals with a global mortality of 5922047 people as of February 25, 2021[2]. Considering the massive spikes in cases of COVID-19 across countries within a short period of time, the World Health Organization declared COVID-19 as a public health emergency of international concern, giving it a global risk assessment of extremely high[3]. SARS-CoV-2 primarily infects respiratory tract cells and manifests as mild to fatal pneumonitis[4], especially in older men with comorbidities of hypertension, diabetes mellitus, or vascular disease[5].

SARS-CoV-2 is an enveloped virion with positive sense, single-stranded RNA with a genome size of 29.99 kb encoding for multiple nonstructural and structural proteins. The viral envelope contains four anchored structural proteins, spike protein (S), enveloped protein (E), nucleocapsid protein (N) and membrane protein (M)[6]. S glycoprotein (type 1 transmembrane protein) protrudes from the virus surface and embraces two functional components, S1 and S2. S1 helps the virus to binds with host cell through its receptor-binding domain (RBD) and S2 possesses an element essential for SARS-CoV-2 fusion with the host cell membrane[7].

SARS-CoV-2 enters type II pneumocytes in the lungs by binding with membrane-bound angiotensin-converting enzyme (ACE) 2 receptor through its RBD[6], primed by host cell surface transmembrane serine protease-2[8]. SARS-CoV-2 then starts replicating and migrating down to the airways and enters alveolar epithelial cells in the lungs, resulting in pre-eminent early viral loads and soluble ACE2 (sACE2) protein release into the bloodstream[9]. Cumulative viral load destroys type II alveolar epithelial cells and decreases the synthesis of pulmonary surfactants[10]. Simultaneously, infiltration of macrophages causes secretion of various cytokines namely tumor necrosis factor (TNF)-α, interleukin (IL)-1 and IL-6, instigating migration of lymphocytes and neutrophils and vasodilatation. This dysregulated host immune response plays a crucial role in the pathogenesis of the cytokine storm in SARS-CoV-2 infection[11].

Common clinical manifestations of SARS-CoV-2 infection are pyrexia, tussis, dyspnea, pharyngitis, myalgia, headache, and olfactory and taste dysfunction (hyposmia/anosmia or ageusia)[12]. However, severe consequences such as viral sepsis have been observed in approximately 20% of SARS-CoV-2-infected patients. Sepsis is a life-threatening systemic condition that graduates to cytokine storm followed by immune dysregulation, leading to systemic hyperinflammatory state, acute respiratory distress syndrome (ARDS), multiorgan failure, and development of sepsis-related complications with increased mortality[13].

Apart from inflammation and virulence, tissue tolerance and host response are also important factors for the pathogenesis and resultant consequences of SARS-CoV-2 infection[14]. A member of the transforming growth factor-β superfamily, growth and differentiation factor (GDF)-15, is a multifunctional anti-inflammatory cytokine that increases immunotolerance physiologically. It is an evolving modulator of immune responses and facilitates inflammation-induced tissue tolerance through metabolic adaptation[15,16]. Various pathways such as inflammation, hypoxia and oxidative stress tightly regulate expression of GDF-15[17]. In an animal model infected by human rhinovirus, GDF-15 promotes viral replication and virus-induced inflammation in the lungs[18]. Thus, GDF-15 may attenuate the antiviral immune response and affect the consequences of SARS-CoV-2 infection. Conversely, GDF-15 might increase in SARS-CoV-2 infection due to the altered balance of proinflammatory and anti-inflammatory cytokines[14].

Some biomarkers, such as C-reactive protein (CRP), D-dimer, ferritin[19] and presepsin[20], have been identified as biomarkers to assess the inflammation and consequences of SARS-CoV-2 infection. However, more than a year into the pandemic with little evidence of specific therapeutic regimens, front-line clinicians are still reliant on clinical presentation and basic imaging facilities for assessing risk stratification of SARS-CoV-2[21]. Since there are limited data on the accuracy of laboratory investigations for evaluating the severity of SARS-CoV-2 infection[22], identifying a novel biomarker such as GDF-15 offers the opportunity to triage patients for disease severity, allowing better care and timely management of critical patients. As GDF-15 predicts tissue tolerance in SARS-CoV-2-induced inflammation[14], it is worth reviewing the importance of GDF-15 for diagnosis and risk stratification of SARS-CoV-2. This systematic review emphasizes the importance of GDF-15 in SARS-CoV-2 infection by providing the most current evidence from studies that have examined GDF-15 in SARS-CoV-2 patients.

MATERIALS AND METHODS

Literature search strategy

The highly sensitive systematic literature search was carried out in multiple electronic databases: PubMed, Reference Citation Analysis (RCA), China National Knowledge Infrastructure (CNKI), Web of Science and Google Scholar. The following MeSH keywords were used to search the literature: GDF-15 AND SARS-CoV-2 OR GDF-15 AND COVID-19 OR GDF-15 AND 2019-nCoV OR GDF-15 AND Coronavirus Disease 2019. The inclusion criteria were English language articles published between December 1, 2020 and February 15, 2022. The original research articles, case series, brief reports, and letters were accepted for review. All selected articles' reference list was further screened to identify additional possible research literature. There was no exclusion based on the study outcome and stage or severity of SARS-CoV-2 infection. Finally, seven out of 24 articles were selected for the review after removing the duplicate research literature.

Data extraction

Using the above key terms, the first two authors independently searched for research literature following the inclusion and exclusion criteria, and both authors selected the final articles. The data were extracted in duplicate by standardized data extraction tables by two researchers. The following data were extracted: first author, place of study, sample size, disease severity/stage, intensive care unit (ICU) admission, survivors and nonsurvivors/death, GDF-15 level, and correlation with other inflammatory or sepsis biomarkers.

RESULTS

A total of 14 studies were retrieved after removing the duplicate or repeated publications; 13 of which were evaluated in full text. Among the included studies, seven were considered suitable for the qualitative synthesis. The process flow for the extraction of research literature (Figure 1) was conducted according to the guidelines defined in the PRISMA statement 2020 and was performed in accordance with a predetermined published protocol (PROSPERO ID: CRD42022311838).

DISCUSSION

The primary analysis of this systematic review revealed a high level of GDF-15 in SARS-CoV-2-infected patients and found a significant interaction with the severity of COVID-19. GDF-15 was also found to be positively correlated to predict the disease severity and to some degree is worthier than other inflammatory biomarkers as CRP, D-dimer, procalcitonin and ferritin. This conclusion came firstly from the study by Myhre and colleagues in 2020, which evaluated the utility of serum GDF-15 as a prognostic biomarker in hospitalized patients with SARS-CoV-2, and compared it with other known inflammatory

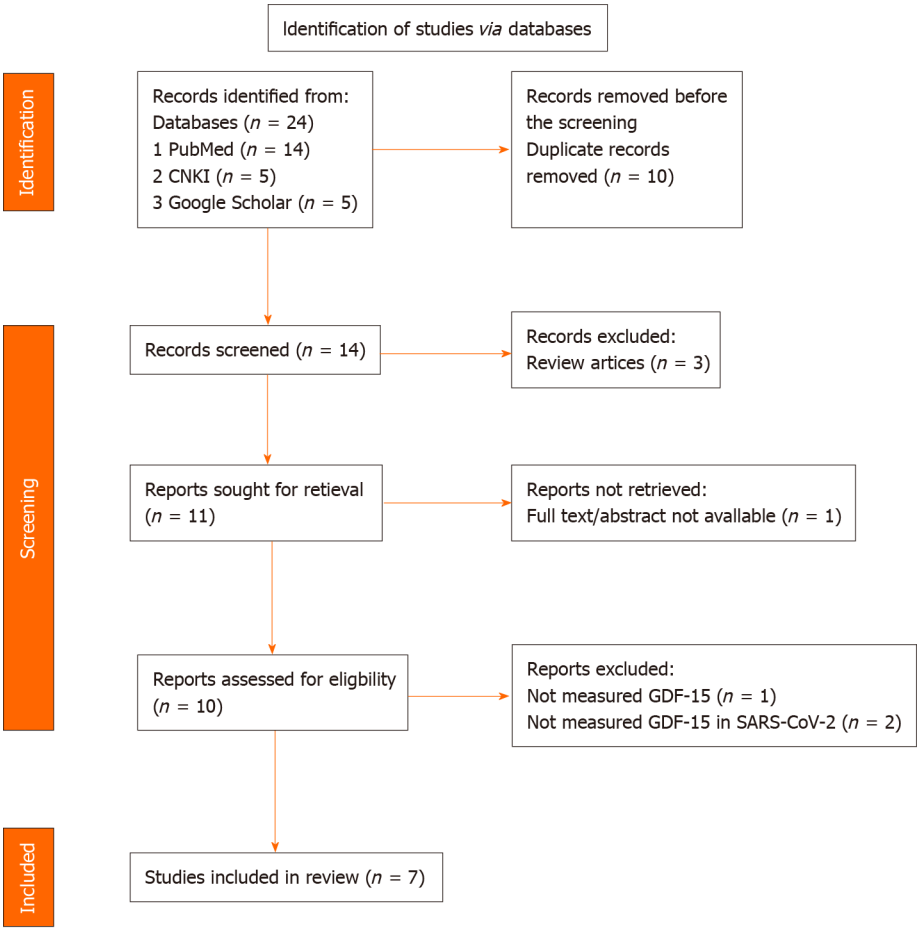

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Figure 1 Flow diagram for selection of research studies from various databases according to PRISMA 2020 guidelines. SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2.

biomarkers (CRP, D-dimer, IL-6, procalcitonin and ferritin) in the Norwegian population from March 18, 2020 to May 4, 2020. The baseline GDF-15 level was elevated in 78% of cases of SARS-CoV-2 infection and it was found to be associated with viral load and hypoxemia. The GDF-15 concentrations were higher in patients who met the primary endpoint of ICU admission or death [4225.0 (3197.0–5972.0) pg/mL *vs* 2187.0 (1344–3620.0) pg/mL, $P < 0.001$]. Patients who reached the primary endpoint had a significant rise in GDF-15 from baseline to day 3 [86.0 (322.0–491.0) *vs* 1208.0 (0–4305.0) pg/mL, $P < 0.001$]. The area under the receiver operating characteristic curve (ROC) was 0.78 (95% confidence interval = 0.70–0.86), indicating a better prognostic significance of GDF-15 than for recognized inflammatory biomarkers such as CRP, ferritin, procalcitonin and IL-6. They derived a cut-off value of 2252.0 pg/mL that differentiated non-ICU survivors from nonsurvivors or ICU admission with good accuracy [23].

Secondly, Notz *et al*[24] measured blood GDF-15 in patients with SARS-CoV-2-induced ARDS in the German population from March 14 to May 28, 2020 and reported an increased level of GDF-15 in patients during their ICU stay. In addition, they testified that comorbidities were unlikely to influence the blood GDF-15 levels, and GDF-15 was not correlated with age, BMI or other anthropometric variables of patients[24]. Subsequently, Luis García de Guadiana Romualdo *et al*[25] evaluated the effect of circulating GDF-15 levels to predict the mortality of hospitalized SARS-CoV-2-infected patients in the Swedish population from March 14 to April 12, 2020. They found a significantly elevated level of GDF-15 in nonsurvivors compared to survivors of SARS-CoV-2 infection [9448.0 (6462.0–11707.0) *vs* 2590.0 (1886.0–4811.0) pg/mL]; a superior discriminatory ability of GDF-15 to predict in-hospital mortality at the cut-off value ≥ 7789.0 pg/mL [AUC = 0.892 (0.792–0.955), $P < 0.001$]. GDF-15 levels were also positively correlated with CRP ($r = 0.527$; $P < 0.001$), ferritin ($r = 0.334$; $P = 0.006$) and D-dimer ($r = 0.260$; $P = 0.035$). They concluded that GDF-15 might be used to predict the prognosis of in-hospitalized patients with SARS-CoV-2[25].

Likewise, Teng *et al*[26] retrospectively evaluated the profile of inflammatory factors in SARS-CoV-2-infected patients and healthy controls in China from January 22 to May 13, 2020. They assessed GDF-15 by categorizing SARS-CoV-2 patients into asymptomatic, mild, moderate, severe and convalescent; GDF-15 at admission, remission and discharge to find the association between dynamic alteration in

GDF-15 with the progression of SARS-CoV-2 infection, and found that GDF-15 concentration escalated consistently with disease severity. GDF-15 expression returned to normal in the convalescent group, as it did in the healthy participants. In continuance, study data revealed GDF-15 levels acutely upsurged with the worsening of symptoms before death, inferring that GDF-15 aptly monitors progression of SARS-CoV-2 infection. They reported an AUC value of 0.89 for GDF-15, which implied that the serum GDF-15 is an effective diagnostic biomarker to assess the severity of SARS-CoV-2 infection[26].

A prospective study conducted in the Swedish population[27] to evaluate the GDF-15 in SARS-CoV-2-infected patients and healthy controls reported a significantly ($P < 0.001$) higher level of GDF-15 in the severe [3562.0 pg/mL (2458.0–5880.0)] and moderate [3450.0 pg/mL (2337.0–4105.0)] type of SARS-CoV-2 infection compared to mild infection [748.0 pg/mL (586.0–1087.0)] and healthy participants [703.0 pg/mL (501.0–949.0)] throughout the acute phase. In the follow-up visit at 6 mo, severe and moderate SARS-CoV-2 infection was recorded with a high GDF-15 level compared to mild type and healthy controls ($P < 0.05$). Like the findings of Myhre *et al*[23], these authors also reported a significant association of GDF-15 with hypoxemia, viral load, and worse clinical consequences in SARS-CoV-2 infection[27].

Ebihara *et al*[28] conducted a prospective, multicenter observational study in the Japanese population to evaluate the role of cytokines in the pathogenesis of SARS-CoV-2 infection, through proteomics analysis. They found: an increased level of GDF-15 in patients with SARS-CoV-2 infection during ICU stay; an AUC of 0.764 and 0.740 for SARS-CoV-2 infection severity and prognosis, respectively; plasma level of GDF-15 was significantly associated with the time to wean off mechanical ventilation and delay recovery in ICU. Based on these results, the authors concluded that GDF-15 was positively related to the severity of SARS-CoV-2 infection and its concentration was significantly higher in patients with sepsis compared with SARS-CoV-2 infection[28].

Alserawan *et al*[29] evaluated serum GDF-15 level and correlated it with SARS-CoV-2 infection severity in the Spanish population. They reported a significantly ($P < 0.0001$) higher level of GDF-15 in SARS-CoV-2-infected patients [2051.0 (1474.0–2925.0) pg/mL] compared to healthy controls [582.0 (370.0–807.0) pg/mL] and in patients who were admitted to hospital for > 9 d. They categorized SARS-CoV-2 patients into $SpO_2/FiO_2 \leq 400$ and > 400 to find an association of GDF-15 with lung involvement. They found high GDF-15 levels in SARS-CoV-2-infected patients with $SpO_2/FiO_2 \leq 400$ or lung impairment. GDF-15 concentrations ≥ 1675.0 pg/mL were found to be a good predictor for impaired pulmonary function or $SpO_2/FiO_2 \leq 400$ compared with CRP and D-dimer, according to ROC analysis (AUC = 0.729, $P < 0.002$)[29]. Wallentin *et al*[30] observed that GDF-15 was associated with sACE2 levels, increased risk of mortality, and cardiovascular disease, which could help identify those at risk for severe COVID-19 infection.

Table 1 abridges the findings of included studies in this systematic review and Table 2 gives an overview of the data pertaining to GDF-15 in the included studies. Gleaned from the included studies, we conclude that GDF-15 has both diagnostic and prognostic importance in SARS-CoV-2 infection. As SARS-CoV-2 invades the lungs, it causes leukocyte migration, endothelialitis, hypoxia and tissue destruction by enhanced innate immunity[31]. All these factors promote secretion of GDF-15 from infected alveolar epithelial cells. Migration of leukocytes releases proinflammatory cytokines such as TNF-α, IL-8, IL-6, IL-1β, interferon- and granulocyte–macrophage colony-stimulating factor, which in turn stimulates the Notch pathway. The Notch pathway may well activate the Wnt and Hippo pathways, which, in succession cause differentiation of IL-17- and GDF-15-mediated inhibition of the T regulatory suppressor cell activity, respectively, which individually and in conjunction with one another results into extreme activation of the immune system. Concurrently, syncytical development further hyperactivates the immune system and results in a cytokine storm. Thus, GDF-15 plays a pivotal role in the immunological context and may influence the pathogenesis of SARS-CoV-2[14,32].

Impaired iron metabolism has also been hypothesized in the development of hyperinflammation and oxidative stress in patients with SARS-CoV-2 infection. GDF-15 has also been found to interact with iron metabolism, hepcidin and erythropoiesis during inflammation. More specifically, elevated GDF-15 during hypoxia and anemia has been found to suppress hepcidin expression, which boosts the iron level for hemoglobin production. As a result, GDF-15 has been considered as an immune modifier to regulate altered erythropoiesis and ferroptosis in patients with SARS-CoV-2 infection with anemia. During inflammation, GDF-15 overexpression has been associated with iron overload, which could increases ferritin, another key biomarker to assess severity of SARS-CoV-2 infection[33]. Hence, this hypothesis supports the association between high GDF-15 and anemia in inflammatory conditions such as SARS-CoV-2 infection, chronic kidney disease[34], diabetes, cardiovascular diseases[35], and cancer[36].

The iron chelation therapy improves innate immunity and endothelialitis in SARS-CoV-2 infection through its antifibrotic and antiviral properties[37] and is substantiated by the fact that the US FDA approved iron chelation therapy as an adjuvant treatment for the management of critical patients with SARS-CoV-2 infection[38]. Consequently, GDF-15 could be considered a crucial biomarker to indicate the prompt use of iron-chelating therapy in SARS-CoV-2 infection.

Metformin has recently been shown to elevate blood GDF15 levels, resulting in decreased satiety and body weight in clinical investigations. In animal studies, metformin was also associated with increased GDF-15 levels, along with increased GDF-15 expression in kidneys and intestines. In addition, metformin supplementation decreased weight in high-fat-fed mice, but not in GDF15-deficient mice and

Table 1 Studies included in the systematic review, with duration, type, region/place, and main findings

Refs	Study duration	Type of study	Region/place	Main findings
Myhre *et al*[23], 2020	March 18, 2020 to May 4, 2020	Prospective, observational study	Norway	GDF-15 has a better prognostic significance than recognized inflammatory biomarkers like CRP, ferritin, procalcitonin, and IL-6
Notz *et al*[24], 2020	March 14 to May 28, 2020	A single-center retrospective study	Germany	There was no evident imbalance of pro-and anti-inflammatory pathways, with higher GDF-15 levels in patients with SARS-CoV-2 infection during ICU stay, implying elevated tissue resilience
Luis García de Guadiana Romualdo *et al*[25], 2021	March 14 to April 12, 2020	Case-series	Spain	The GDF level was significantly high in nonsurvivors compared to survivors of SARS-CoV-2 infection, and it may be useful to predict prognosis
Teng *et al*[26], 2021	January 22, 2020, to May 13, 2020	Retrospective study	China	GDF-15 could be used as a biomarker to predict the severity of SARS-CoV-2 infection. GDF-15 level increased consistently with increased severity of SARS-CoV-2 infection, and GDF-15 expression returned to normal level similarly in a convalescent group compared to the healthy control participants. Hence, it implies that the GDF-15 precisely monitors the progression of SARS-CoV-2 infection
Kanberg *et al*[27], 2021	February 21 to November 5, 2020	Prospective study	Sweden	Patients with severe and moderate SARS-CoV-2 infection exhibited significantly increased GDF-15 levels compared with participants with mild infection and controls throughout the acute phase. Even after 6 mo of infection, GDF-15 concentrations persisted considerably higher in the severe and moderate infections compared to patients with mild infection and controls
Ebihara *et al*[28], 2022	August 2020 to December 2020	Prospective multicenter observational study	Japan	GDF-15 may be beneficial to predict delayed recovery or mortality of SARS-CoV-2-infected patients during ICU treatment
Alserawan *et al*[29], 2021	Not mentioned	Prospective study	Spain	GDF-15 may play a role in categorizing SARS-CoV-2-infected patients based on severityGDF-15 is an excellent biomarker to detect impaired respiratory function compared to CRP and D-dimer

CRP: C-reactive protein; GDF-15: Growth differentiation factor 15; IL-6: Interleukin 6; ICU: Intensive care unit; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2.

mice deficient for GFRAL (GDNF family receptor α-like, receptor for GDF-15)[39-42]. Thus, metformin supplementation has been associated with reduction in mortality in patients with SARS-CoV-2 infection with diabetes.

A few limitations of this analysis should be taken into consideration when interpreting the results for any potential clinical implications. Firstly, the sample size was small. Secondly, heterogeneity was a major issue in the included studies, especially in terms of methodology, type of ongoing treatment, time of sample collection after hospital admission, non-consideration of the disease-onset time and divergence in adjusting study variables (age, gender, and various comorbidities). Thirdly, variance in the quantification of GDF-15 and subclassification of patient populations in the included studies. Lastly, the literature search and coverage were limited to articles published in English; languages other than English were not considered for analysis, which is susceptible to a local literature bias. Nevertheless, the goal of this study was not to create a predictive model but to investigate the potential importance of GDF-15 as a novel biomarker[39-42]. Hence, despite these limitations, this systematic review offers vital information on the risk stratification of SARS-CoV-2, which could in the future become an important part of the clinical process.

CONCLUSION

GDF-15 appeared to be an important determinant in the etiopathogenesis of disease and might serve as a predictor for onset and severity of SARS-CoV-2 infection. Hence, GDF-15 can be considered a clinically prominent sepsis biomarker for screening, risk stratification, and monitoring SARS-CoV-2.

Table 2 Review of data extracted for growth differentiation factor 15 in SARS-CoV-2 infection from included studies

Refs		Myhre *et al*[23], 2020	Notz *et al*[24], 2020	Luis García de Guadiana Romualdo *et al*[25], 2021	Teng *et al*[26], 2021	Kanberg *et al*[27], 2021	Ebihara *et al*[28], 2022	Alserawan *et al*[29], 2021
Sample size and subgroup of participants, if any		123 confirmed cases of SARS-CoV-2 infection (non-ICU survivor = 88, ICU admission/ death = 28)	13 cases of SARS-CoV-2 infection with ARDS	66 confirmed cases of SARS-CoV-2 infection (non-survival = 58, survival = 6)	111 confirmed cases of SARS-CoV-2 infection and 20 healthy controls (asymptomatic = 14, mild = 12, moderate = 34, severe = 18, and convalescent = 33)	100 confirmed cases of SARS-CoV-2 infection (mild = 24, moderate = 28, severe = 48] and 51 healthy controls	306 confirmed cases of SARS-CoV-2 infection	84 confirmed cases of SARS-CoV-2 infection and 20 healthy controls
GDF-15 level in pg/mL	Healthy controls				13.5 (8.0–79.0)	703.0 (501.0–949.0)	-	582.0 (370.0-807.0)
	Mild				136.4 (44.7–321.4)	748.0 (586.0–1087.0)	-	2051.0 (1474.0-2925.0)
	Moderate		12400.0		256.2 (76.1–341.0)	3450.0 (2337.0–4105.0)	-	
	Severe			-	524.8 (405.1–831.1)	3562.0 (2458.0–5880.0)	Increased during ICU stay	
	Critical				621.0	-	-	-
	Non-ICU survivor	2187.0 (1344.0-3620.0)	-	2590.0 (1886.0-4811.0)	-	-	-	
	ICU admission or death	4225.0 (3197.0-5972.0)	-	9448.0 (6462.0-11707.0)	-	-	-	-
AUC and 95% CI of GDF-15 in ROC analysis		0.78 (0.70–0.86) $P < 0.001$	Not mentioned	0.89 (0.792–0.955) $P < 0.001$	0.89	Not mentioned	For severity: 0.764; For prognosis: 0.740	0.729 (0.602-0.857) $P = 0.002$
The optimal cut-off value of GDF-15		2252.0 pg/mL, to differentiate non-ICU survivors and ICU admission or death	Not mentioned	7789.00 pg/mL, to differentiate non-ICU survivors and ICU admission or death	Not mentioned	Not mentioned	Not mentioned	1675.0 pg/mL, to recognize deprived respiratory function ($SpO_2/FiO_2 \leq 400$)
Method of GDF-15 measurement		ELISA	ELISA	Electro-chemiluminescent	ELISA	Electro-chemiluminescent	ELISA	ELISA
Additional findings related to GDF-15		It was associated with viral load and hypoxemia. Better prognostic significance compared to CRP, ferritin, IL-6, and procalcitonin	It was not correlated with age and BMI	Positively correlated with CRP, ferritin, and D-dimer	GDF-15 indicates the severity and closely monitor the progression of SARS-CoV-2	Elevated GDF-15 was significantly related to hypoxemia, viral load, and worse clinical consequences	The plasma level of GDF-15 was significantly associated with the time to wean-off mechanical ventilation	Positively correlated with CRP, D-dimer, and neutrophil count and negatively correlated with lymphocyte count

ARDS: Acute respiratory distress syndrome; BMI: Body mass index; CRP: C-reactive protein; ELISA: Enzyme-linked immunosorbent assays; GDF-15: Growth differentiation factor 15; IL-6: Interleukin 6; ICU: Intensive care unit; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2.

ARTICLE HIGHLIGHTS

Research background

Growth differentiation factor (GDF)-15 is a modulator of immune responses and facilitates inflammation-induced tissue tolerance through metabolic adaptation. Experimental studies reveled that GDF-15 promotes virus replication and virus-induced inflammation in the lungs. Thus, GDF-15 may attenuate the antiviral immune response and affect the consequences of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.

Research motivation

To identify a novel biomarker for the guidance of severity of disease, so as to provide better care and timely management of critical patients.

Research objectives

To investigate the utility of GDF-15 in predicting the risk stratification of SARS-CoV-2.

Research methods

A systematic literature search was carried out in multiple electronic databases: PubMed, Reference Citation Analysis, China National Knowledge Infrastructure (CNKI), Web of Science and Google Scholar using MeSH keywords. The inclusion criteria were research articles of any type written in the English language and published between December 1, 2020 and February 15, 2022. There was no exclusion based on the study outcome and stage or severity of SARS-CoV-2 infection. Finally, seven of 24 articles were selected for the review after removing the duplicate research literature.

Research results

The primary analysis of this systematic review revealed a high level of GDF-15 in SARS-CoV-2-infected patients and found a significant interaction with the severity of COVID-19. GDF-15 was also found to be positively correlated to predict the disease severity and is superior to other inflammatory biomarkers such as C-reactive protein, D-dimer, procalcitonin and ferritin.

Research conclusions

Serial estimation of GDF-15 levels in hospitalized patients with SARS-CoV-2 infection may have useful prognostic value and GDF-15 can be considered a clinically prominent sepsis biomarker for screening, risk stratification, and monitoring SARS-CoV-2.

Research perspectives

Additional prospective studies are warranted in this regard to justify GDF-15 as an ideal biomarker which should provide optimization of disease status.

FOOTNOTES

Author contributions: Parchwani D and Dholariya S contributed equally to this work from the design of study, search and scrutiny of articles, analysis and manuscript writing to proof reading; Katoch CDS designed the research study, scrutiny of articles and manuscript writing; Singh R literature search and analysis; all authors have read and approve the final manuscript.

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META-ANALYSIS

Microvessel density in differentiated thyroid carcinoma: A systematic review and meta-analysis

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Abstract

BACKGROUND

Microvessel density (MVD) has been proposed as a direct quantification method of tumor neovascularization. However, the current literature regarding the role of MVD in differentiated thyroid carcinoma (DTC) remains inconclusive.

AIM

To appraise the effect of tumoral MVD on the survival of patients with DTC.

METHODS

This meta-analysis was based on the PRISMA guidelines and the Cochrane Handbook for Systematic Reviews of Interventions. The electronic databases Medline, Web of Science, and Scopus were systematically screened. A fixed-effects or random-effects model was used, according to the Cochran *Q* test. The data were then extracted and assessed on the basis of the *Reference Citation Analysis* (https://www.referencecitationanalysis.com/).

RESULTS

A total of nine studies were included in the present study. Superiority of low MVD tumors in terms of 10-year disease free survival (OR: 0.21, 95%CI: 0.08–0.53) was recorded. Lowly vascularized thyroid cancers had a lower recurrence rate (OR: 13.66, 95%CI: 3.03–61.48). Moreover, relapsing tumors [weighed mean difference (WMD): 11.92, 95%CI: 6.32–17.52] or malignancies with regional lymph

node involvement (WMD: 8.53, 95%CI: 0.04–17.02) presented with higher tumoral MVD values.

CONCLUSION
MVD significantly correlates with the survival outcomes of thyroid cancer patients. However, considering several study limitations, further prospective studies of higher methodological and quality level are required.

Key Words: Cancer; Density; Microvessel; Thyroid; Vascularization

Core Tip: This systematic review is the first meta-analysis investigating the effect of tumoral vascularity, through microvessel density (MVD) assessment, on the survival of patients with differentiated thyroid carcinoma. Higher intratumoral MVD values were associated with inferior disease-free survival outcomes.

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INTRODUCTION

Thyroid cancer is the most common endocrine tumor and includes several subtypes with different histologic, epidemiologic, and prognostic characteristics. Although they display a stable mortality rate, thyroid carcinomas are characterized by a rising trend of overall incidence of nearly 5.5% annually[1-3]. The above-mentioned increase is primarily attributed to a steady increment of new papillary thyroid cancer cases[1-3]. This is translated to an average of 56000 new cases and 2000 deaths per year in the United States alone[4]. Therefore, an attempt to identify survival-prognostic indicators for thyroid cancer has been implemented[5,6]. More specifically, extrathyroidal infiltration, aggressive histological pattern, vascular invasion, lymph node involvement, distant metastases, and BRAF mutations have been linked to a poorer survival outcome[7,8]. Various other serological, genetic, molecular, and immunohistochemical markers have also been considered[5,6,9-11].

Angiogenesis represents a pivotal part of tumor expansion and metastasis development. It includes a cascade of processes such as degradation of the basal membrane, remodeling of the extracellular matrix, migration of the endothelial cells, and maturation of the newly formed capillaries, which are regulated by several angiogenic and angioinhibitory factors[12-14]. Activation of the "angiogenic switch" due to alterations in the concentration of agents, such as vascular endothelial growth factor (VEGF) and thrombospondin-1 (TSP-1), as well as the subsequent upregulation of the *de novo* formation of blood vessels, has been associated with survival outcomes in thyroid cancer[15,16]. Microvessel density (MVD) as described by Weidner *et al*[17] has been proposed as a direct quantification method of tumor neovascularization. The methodology of MVD assessment involves the immunohistochemical staining for endothelium specific markers, such as von Willebrand factor (vWF), cluster of differentiation (CD)31, and CD34, for the labeling of microvessels[18]. The correlation between survival outcome and vascularity of a solid tumor has been extensively validated[19-22].

The current literature regarding the role of MVD in differentiated thyroid carcinoma (DTC) remains inconclusive. Initial studies reported that MVD displayed negative prognostic value in terms of survival, and was reversibly associated with the differentiation status of thyroid carcinomas[9,23,24]. However, subsequent trials did not confirm the prognostic role of MVD value or even document a positive correlation with survival endpoints[25,26]. Taking into consideration the above-mentioned evidence, a systematic literature review and meta-analysis was designed and conducted to clarify the effect of tumoral vascularity - through MVD assessment - on the survival of patients with DTC.

MATERIALS AND METHODS

Study protocol

This review was performed by applying the guidelines proposed in the PRISMA Statement and the Cochrane Handbook for Systematic Reviews of Interventions[27].

Endpoints

The primary endpoint of the present meta-analysis was the pooled odds ratio (OR) of disease-free survival (DFS) between high and low MVD measurements in patients with DTC[28,29]. Secondary endpoints included the hazard ratio (HR) of DFS and the OR of overall survival (OS) and DFS at specific time endpoints (5 and 10 years). Moreover, the effect of MVD on certain disease outcomes was examined, such as lymph node involvement, extrathyroidal infiltration, and recurrence rates.

Eligibility criteria

All prospective or retrospective studies that included a trial population diagnosed with DTC, reported outcomes of interest in English, and could be retrieved were considered as eligible. The MVD assessment of the primary tumor should have been introduced in the study design. The exclusion criteria for this meta-analysis were studies: (1) Written in a language other than English; (2) With no outcome of interest; (3) With insufficient data; (4) With no human subjects; (5) Including a pediatric study population; (6) Including undifferentiated or medullary thyroid cancer; or (7) In the form of editorials, letters, conference abstracts, or expert opinions.

Literature search

A systematic literature search was performed in the electronic scholar databases Medline, Scopus, and Web of Science. The last search date was August 31, 2021. The following keywords were used: "Thyroid", "thyroid cancer", "thyroid carcinoma", "papillary", "follicular", "Hurthle cell", "well differentiated", "MVD", "microvessel density", "microvascular density", and "vessel density".

Study selection and data collection

The first step of our review was removal of duplicate entries, followed by screening of titles and abstracts for consistency with the eligibility criteria. The remaining articles were submitted to a full text review. Searching of electronic databases, study selection, data extraction, and methodological assessment of the studies were performed blindly and in duplicate by two independent investigators (Perivoliotis K, Koutoukoglou P). If disagreement arose between the two investigators, a mutual revision and discussion process followed. If consensus was not achieved, the opinion of a third researcher was considered (Ntellas P). The methodological and quality evaluation was performed on the basis of the Newcastle-Ottawa Scale (NOS)[30]. This evaluation tool ranks non-RCT trials based on different domains, such as selection and comparability of the study groups and confirmation of the exposure. All eligible studies were rated with a score ranging from 0 to 9. Interrater agreement was estimated based on Cohens *k* statistic.

Statistical analysis

The statistical software used for the analyses included the Cochrane Collaboration RevMan version 5.3 and IBM SPSS version 23. All results are presented with the corresponding 95%CI. If the trials included did not directly provide data concerning the HR and OR endpoints, they were then estimated through the implementation of the algorithm proposed by Parmar *et al*[31] and Tierney *et al*[32]. By utilizing digitizing software, an accurate reconstruction of the primary data from the Kaplan-Meier (KM) curves was performed[33,34]. Furthermore, if the mean and standard deviation (SD) of the continuous variables were not reported, they were estimated from the respective median, range, or interquartile range (IQR)[35,36].

The statistical methods applied were the Maentel-Haenszel (MH) and inverse variance (IV), for OR and HR, respectively. If a statistically significant heterogeneity was present (Cochran Q test $P < 0.1$), a random-effects (RE) model was used. Otherwise, the pooled result estimation was based on a fixed-effects (FE) model. Overall heterogeneity was also quantified through the calculation of I^2. Statistical significance was considered at the level of $P < 0.05$.

Risk of bias across studies

Visual inspection of the primary outcome funnel plot was applied, to identify possible outliers. Moreover, Egger's statistical test was calculated.

RESULTS

Study selection

Application of the search algorithm resulted in the retrieval of 2208 citations (Figure 1). More specifically, the number of studies identified through Medline, Scopus, and Web of Science were 992, 517, and 699, respectively. After removal of 507 duplicate records, 1701 titles and abstracts were reviewed. In this phase of literature screening, 1626 studies (125 non-human studies, 130 reviews or meta-analyses, and 1371 irrelevant trials) were excluded. Full text review was applied to 75 articles to assess consistency with the inclusion criteria. After the exclusion of 50 irrelevant records and 16 studies

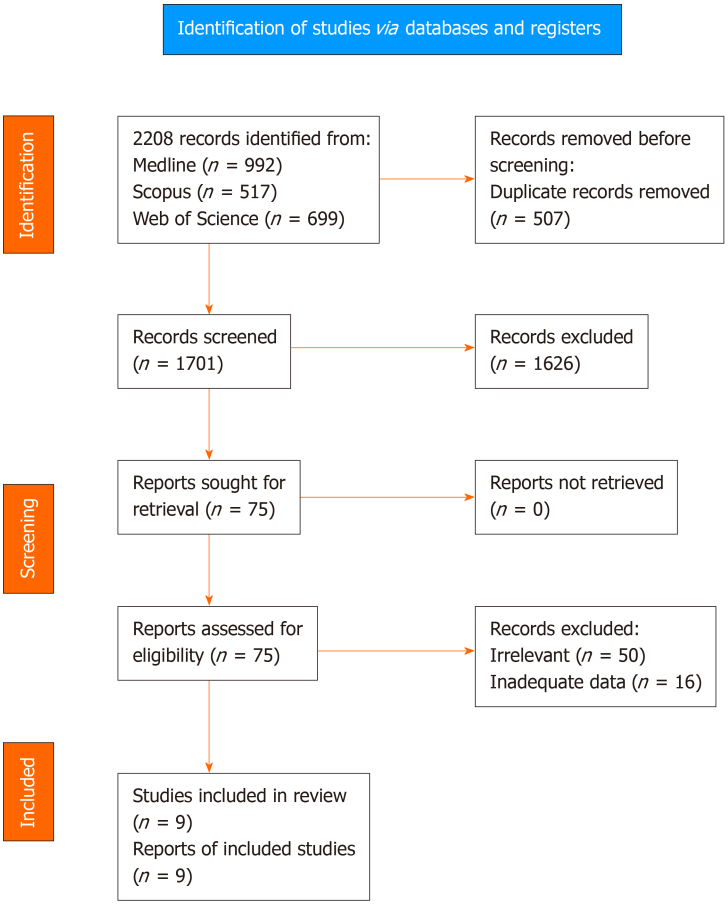

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Figure 1 Study flow diagram.

with inadequate survival data, a total of nine trials[23,25,37-43] were introduced in the qualitative and quantitative synthesis of the present systematic review.

Study characteristics

Table 1 summarizes the characteristics of studies included in the systematic review. Concerning the study design, all trials were retrospective and single centered, with publication years ranging from 1998 to 2017. In total, 738 patients were included in this meta-analysis. Mean age and gender allocation are also presented in Table 1. Mean follow up extended from 61.7 mo to 180 mo.

Supplementary Table 1 provides information regarding the tumor characteristics. The most frequent malignancy was papillary thyroid carcinoma (PTC) (708 cases), followed by follicular thyroid carcinoma (FTC) (27 cases). Although data regarding the tumor stage and the TNM classification were scarce and inconsistent, the respective allocations are also displayed.

Regarding MVD assessment method (Supplementary Table 2), in the majority of the articles[23,25,37,39,40], the technique proposed by Weidner *et al*[17] was implemented. In the remaining studies[38,41-43], variations of the hot spot method, such as the methodology described by Bono *et al*[44], were applied. The antibodies used for the immunochemical staining of the microvessels included the anti-CD34[35-39], anti-CD31[42,43], and anti-VIII antibodies[23,25]. The initial magnification applied spanned from 4 × to 40 ×, whereas the final magnification included values ranging from 200 × to 400 ×. The number of pathologists and hot spots examined varied among studies, thereby increasing the methodological heterogeneity. Blinding of the MVD estimator was applied in four trials[23,37,40,43]. Assessment of both intra- and peri-tumoral vessels was performed in only two studies[25,40]. Furthermore, the MVD cut off values are included in Supplementary Table 2. Overall, 324 total or subtotal thyroidectomies and 71 lobectomies were performed Supplementary Table 3). Lymph node dissection was reported in 574 cases. Data regarding the adjuvant chemotherapy or radiotherapy mode were not systematically provided.

Risk of bias within studies

Supplementary Table 4 provides a detailed report on the quality and methodological evaluation of the included trials. Although the number of stars awarded ranged from 3[39] to 7[42], the majority of trials

Table 1 Study characteristics

Ref.	Type of study	Year	Country	Center	Sample (patients)	Age	Gender (male/female)	Follow-up
Lee *et al*[36]	Retrospective	2017	Korea	Single center	202	43.4 (13.6)	43/159	NA
Liu *et al*[37]	Retrospective	2017	China	Single center	42	49.1 (13.5)	9/33	NA
Hakala *et al*[40]	Retrospective	2014	Finland	Single center	51	52	19/32	NA
Lee *et al*[41]	Retrospective	2012	Korea	Single center	47	> 45: 24	11/36	NA
Yasuoka *et al*[38]	Retrospective	2005	Japan	Single center	49	48.8 (15)	7/42	NA
Kilicarslan *et al*[39]	Retrospective	2003	Turkey	Single center	48	39.8	21/27	61.7 (29.7)
Akslen *et al*[25]	Retrospective	2000	Norway	Single center	128	45.1	36/89	145 (35.8)
Dhar *et al*[35]	Retrospective	1998	Japan	Single center	71	50 (9.8)	11/60	180 mo
Ishiwata *et al*[23]	Retrospective	1998	Japan	Single center	100	48 (9.6)	5/95	101 mo

NA: Not available.

received a 5 star grade. A satisfying rate of interrater agreement was identified (Cohen's k: 72.1%, P < 0.001).

Primary endpoint

Data regarding the primary outcome were extracted from three studies (Figure 2). Pooled analysis of these data showed a statistically significant OR (P < 0.001) for DFS between high and low MVD groups (OR: 0.21, 95%CI: 0.08–0.53). Heterogeneity levels were not significant (Q test P = 0.12, I^2=53%) and as a result, a FE model was applied. Due to the small number of studies reporting on the primary outcome and the moderate heterogeneity, further sub-analyses included only sensitivity analysis Supplementary Figure 1).

Secondary endpoints

In accordance with the primary outcome, a statistically significant OR for DFS at 5 years (Figure 1) was identified (P = 0.004). Therefore, overall HR (P < 0.001) for DFS was in favor of the low vascularity group (HR: 6.31, 95%CI: 2.81–14.17). However, meta-analysis of the raw data at 10 years postoperatively did not show a significant difference in survival terms (10-year OS: OR: 0.78, 95%CI: 0.01–61.19, P = 0.91). In total, five studies (Figure 3) provided data regarding mean MVD measurements between tumors with positive and negative lymph nodes. Although heterogeneity was high (Q test P < 0.001, I^2 = 93%), tumors that involved lymph nodes had higher mean MVD measurements (weighed mean difference [WMD]: 8.53, 95%CI: 0.04–17.02, P = 0.05) when compared to DTCs with negative nodes. Despite this, extrathyroidal infiltration was not associated with tumoral vascularity (OR: 1.86, 95%CI: 0.56–6.15, P = 0.31). Finally, recurrence rates in DTCs were significantly higher in the highly vascularized tumors (OR: 13.66, 95%CI: 3.03–61.48, P = 0.0007). Besides this, the thyroid malignancies that relapsed had significantly higher mean vascularization values (WMD: 11.92, 95%CI: 6.32–17.52, P < 0.001) than those that did not recur.

Risk of bias across studies

Concerning the funnel plot of the primary outcome Supplementary Figure 2), eligible trials were symmetrically distributed on both sides of the combined effect size line. Moreover, Egger's test did not confirm the presence of a significant publication bias (P = 0.585).

DISCUSSION

Our study validated a negative linkage between the intratumoral vascularity and the survival outcomes in DTC. Specifically, higher MVD values translated to a lower HR of DFS. In a similar manner, the DFS probabilities at 5 and 10 years after diagnosis increased when the DTC was hypovascularized. Furthermore, lymph node metastases were associated with a denser microvessel plexus in the primary tumor. In terms of recurrence, higher MVD measurements were correlated to superior relapse rates and *vice versa*. The rate of extrathyroidal invasion, however, did not appear to be affected by the tumor vascularization pattern. The effect of microvessel quantity in thyroid carcinoma is still a matter of controversy[16]. In 1994, Herrmann and his colleagues reported that reduced vascularization was found in less differentiated tumors[9]. Similarly, according to Kavantzas *et al*[45], FTCs and medullary thyroid

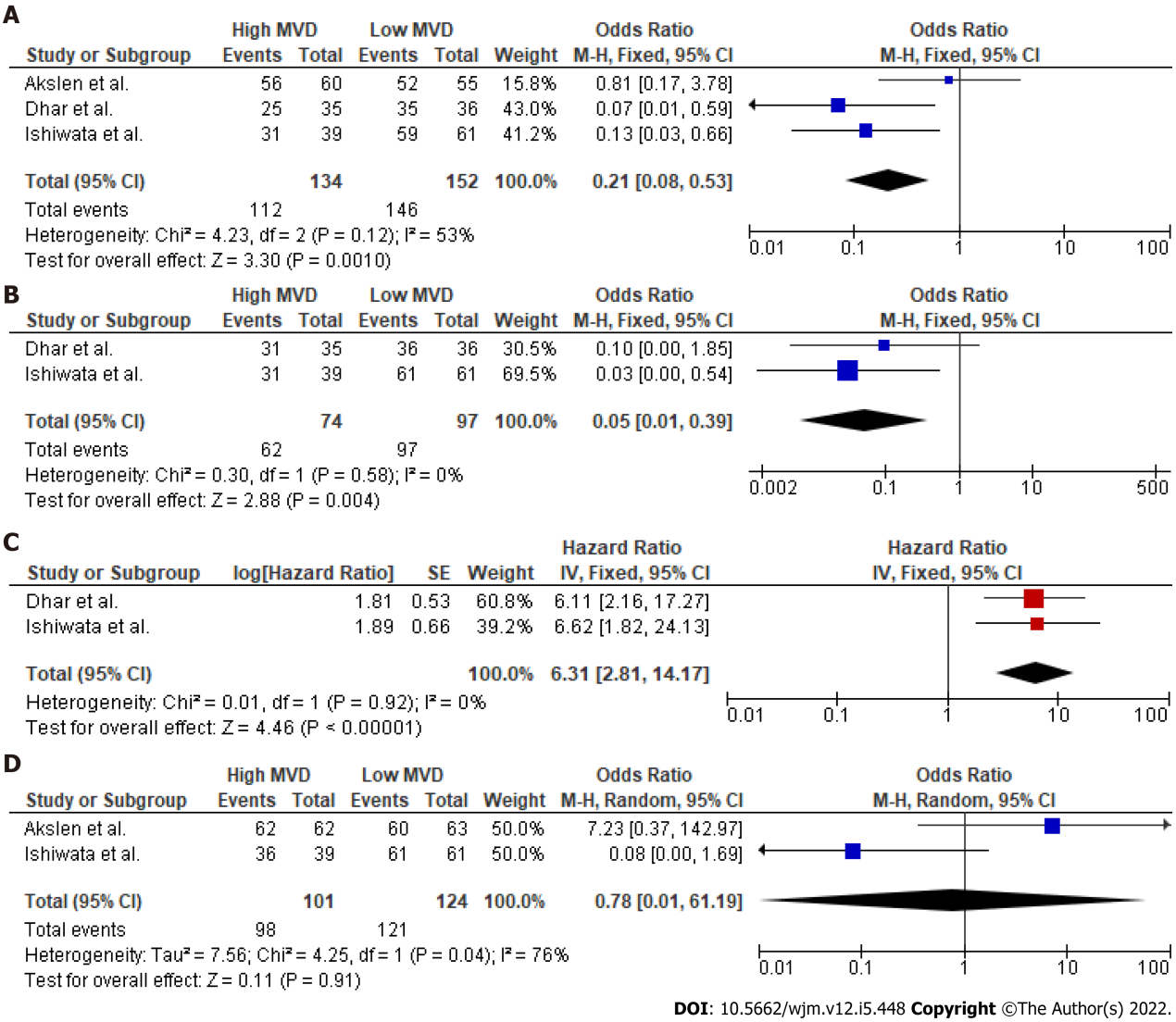

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Figure 2 Survival endpoints. A: 10 year disease free survival (DFS) odds ratio (OR); B: 5 year DFS OR; C: DFS hazard ratio; D: 10 year overall survival OR.

cancers (MTCs) were characterized by different mean MVD values. Diversity in the neovascularization pattern was also found among the differentiated carcinomas. Giatromanolaki *et al*[46] showed that FTCs displayed a higher vascular density, whereas subsequent research by Gulubova *et al*[26] suggested higher CD31 MVD in PTCs. However, several successive studies which applied either a CD34 or CD31 immunohistochemical marker for staining of the endothelium, could not identify a correlation between MVD and histology[10,11].

The fact that most of our quantitative comparisons were statistically significant suggests a possibly strong overall correlation between MVD and prognosis in DTCs. In a retrospective analysis of 71 DTCs, Dhar *et al*[37] correlated a lower recurrence free survival rate with a hypervascularized tumor. Correspondingly, using VIII-related immunohistochemical stain, Ishiwata *et al*[23] identified mean microvessel count as an independent prognostic factor for DFS. A denser angiogenetic pattern was also reported in tumors with a higher metastatic potential[47]. Additionally, MVD has been found significantly higher in malignancies with high risk characteristics, such as extrathyroidal and vascular invasion[48].

In contrast to the above-mentioned statements, a considerable number of studies do not recognize the prognostic character of MVD in thyroid carcinomas. Goldenberg *et al*[11] showed that although mean vessel density in the tumor was higher when compared to the healthy surrounding tissues, MVD lacked a significant correlation with histology or recurrence rates. Furthermore, in the study by Gulubova *et al*[26], postoperative survival rates in PTC patients were not associated with MVD values. Lee *et al*[43] also suggested that lymph node status was not linked to the MVD value of the primary malignancy. Moreover, in a study by Akslen *et al*[25], higher MVD was associated with improved OS rates in PTC patients.

The process of angiogenesis and the corresponding modulators have been extensively studied and related to MVD in thyroid carcinoma. VEGF was directly linked to the number of microvessels, and was characterized as a negative prognostic index for lymph node metastasis as well as local and distant

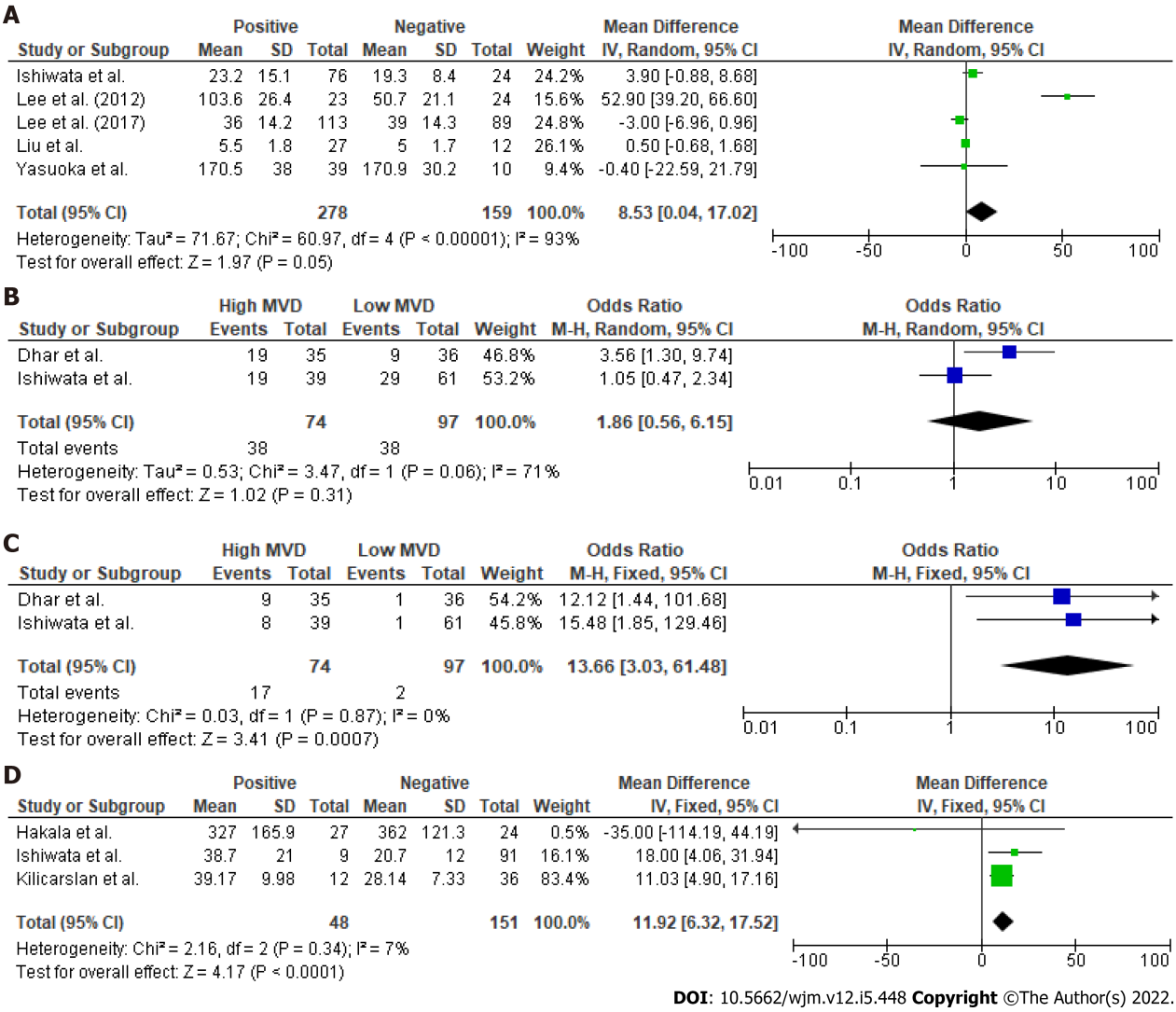

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Figure 3 Secondary endpoints. A: Lymph node involvement; B: Extrathyroidal involvement; C: Recurrence rate; D: Recurrence microvessel density value.

recurrence[26,40,41,43]. A higher rate of immunoreactive cells for metalloproteinase-9, an enzyme necessary for collagen degradation and subsequent angiogenesis, were present in advanced stages of FTCs[14]. Increased values of circulating and tumoral angiopoietins (Ang) have also been linked to poorer outcomes in thyroid cancer[49-51]. Based on the work of Tanaka *et al*, the levels of TSP-1 have been inversely correlated with the infiltration status of the tumor and MVD[52]. As a result, ratios representing the balance of angiogenic and inhibitory factors VEGF/TSP-1, VEGF-C/TSP-1, and Ang-2/TSP-1 have been significantly associated with the number of microvessels[52].

In addition to prognosis, tumor vascularization has also been proposed as a diagnostic tool in thyroid carcinomas. Using color flow Doppler sonographic analysis with a cut off value at 70% of microvessels, differential diagnosis between PTCs and adenomas or adenomatous nodules demonstrated a sensitivity of 92% and specificity of 89%[53]. The administration of contrast agents further validated the correlation of tumoral MVD and ultrasonographic assessment of vascularity, and increased the accuracy of PTC detection at the level of 95.9%[54,55]. In addition, the application of a shear elastography model by Gu *et al*[56] linked tumor stiffness with MVD values. Therefore, subsequent studies examined the role of the relationship between ultrasound estimation of vascularity and MVD, as a potential prognostic and risk assessment factor[38,39].

Before assessing the results of our meta-analysis, several limitations should be appraised. First, only a limited number of studies with a small sample size were introduced in each comparison, thus compromising the validity of our estimations. Moreover, all eligible studies had a retrospective study design, with a moderate-to-low methodological evaluation. Although significant heterogeneity was identified in only two endpoints, bias could be introduced from the non-homogeneous stratification of factors such as the histopathological subtype, the stage, and the TNM status. Another source of potential bias could be the heterogeneous allocation in operative and adjuvant treatment modules. Inconsistency was further identified in technical characteristics of the MVD assessment process. Finally, the estimation of survival endpoints required the reconstruction of raw information from the KM curves; therefore, a

small amount of bias was inherent in our data extraction methodology, although this process has been reported and applied in several studies[31,32,57].

The present systematic review and meta-analysis is the first study that attempts to provide a pooled correlation between MVD and survival endpoints in DTC. Higher intratumoral MVD values were associated with inferior DFS outcomes. Moreover, the thyroid malignancies presenting with lymph node infiltration displayed a higher vascularization pattern. Similarly, relapsing thyroid cancers when compared to non-recurring tumors were characterized by a denser microvascular plexus. Our study concludes that there are significant primary indications of a negative relationship between intratumoral MVD and survival outcomes. However, to clarify the exact effect of MVD on thyroid cancer and due to several study limitations, further prospective studies with a larger sample size as well as a higher methodological and quality level are required.

CONCLUSION

MVD significantly correlates with the survival outcomes of thyroid cancer patients. However, considering several study limitations, further prospective studies of higher methodological and quality level are required.

ARTICLE HIGHLIGHTS

Research background

An attempt to identify survival-prognostic indicators for thyroid cancer has been implemented

Research motivation

Microvessel density (MVD) has been used as a direct quantification method of tumor neovascularization

Research objectives

This meta-analysis attempted to clarify the effect of tumoral vascularity - through MVD assessment - on the survival of patients with differentiated thyroid carcinoma (DTC).

Research methods

The present meta-analysis was based on the PRISMA guidelines and the Cochrane Handbook for Systematic Reviews of Interventions.

Research results

Lowly vascularized thyroid cancers had a lower recurrence rate. Moreover, relapsing tumors or malignancies with regional lymph node involvement presented with higher tumoral MVD values.

Research conclusions

MVD significantly correlates with the survival outcomes of DTC patients

Research perspectives

Further prospective studies and randomized controlled trials have to be conducted in order to elucidate the correlation between MVD and prognosis in DTC.

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FOOTNOTES

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LETTER TO THE EDITOR

Radiological evaluation of patellofemoral instability and possible causes of assessment errors: Letter to the editor

Mohamed Kamal Mesregah

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Abstract

This letter to the editor is a commentary on the study titled "Radiological evaluation of patellofemoral instability and possible causes of assessment errors". There are some pertinent structural changes and radiological findings that should be considered in the setting of traumatic knee injuries, as their recognition is of paramount importance.

Key Words: Patellofemoral instability; Radiological evaluation; Sliver sign; Avulsion fractures; Osteochondral lesions; Bone oedema

Core Tip: The radiological diagnosis of patellofemoral instability is pivotal in management as some radiological findings may necessitate surgical intervention. Therefore, image interpretation should be meticulous. Some crucial radiological findings should be considered in the setting of traumatic knee injuries.

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TO THE EDITOR

I read with interest the review article titled "Radiological evaluation of patellofemoral instability and possible causes of assessment errors" by Ormeci *et al*[1], published in the March 2022 issue of *World Journal of Methodology*. The review article focused on the

potential causes of errors that can occur when measuring some radiographic instability factors, including trochlear dysplasia, patella alta, tibial tuberosity-trochlear groove distance, and patellar tilt[1].

I would like to further discuss some pertinent structural changes and radiological findings that should be considered in the setting of traumatic knee injuries, as their recognition is of paramount importance.

On knee radiographs, a small osseous avulsion fracture on the peripheral margin of the medial patellar facet, known as the "sliver sign", may indicate avulsion of the attachment of the medial patellofemoral ligament (MPFL) and potential patellar dislocation[2].

Studies have shown that 30% of these avulsion fractures are only likely to be recognized on the dedicated patellar view; therefore, including a sunrise view in cases of traumatic knee injuries is essential[3]. Moreover, in the case of radiographic avulsion fracture, further evaluation of additional stigmata of previous patellar dislocation by magnetic resonance imaging (MRI) is recommended[4].

Generally, bone edema of the inferomedial aspect of the patella and the lateral femoral condyle and MPFL disruption indicate a recent patellar dislocation[5].

Even after reduction, the patella typically does not fully return to its normal position. MRI usually reveals patella subluxation or tilt in the majority of patients, and medial patellar chondral lesions are seen in more than two-thirds of patients[5,6]. A concave impaction of the inferomedial patella is highly specific for prior dislocation of the patella[7].

Osteochondral lesions of the lateral condyle are present in approximately 40% of patients. The presence of completely separated bone fragments that may appear as intraarticular bodies is an indication of surgery[8].

The radiological diagnosis of patellofemoral instability is pivotal in management as some radiological findings may necessitate surgical intervention. Therefore, image interpretation should be meticulous.

FOOTNOTES

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LETTER TO THE EDITOR

Mouth shield to minimize airborne transmission risk of COVID-19 and other infectious diseases in the dental office

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Abstract

Transmission of coronavirus disease (COVID-19) and other infectious diseases is a significant risk during dental procedures because most dental interventions involve aerosols or droplets that could contaminate the surrounding environment. Current protection guidelines to address the high risk of droplets, aerosols, and airborne particle transmission of COVID-19 in the dental office recommend minimizing aerosol-generating procedures. In this paper, an innovative mouth shield is presented that should minimize water backsplash from the air-water syringe during dental treatment. The mouth shield can be added to the personal protective equipment to provide the dental team with extra protection. It can be made of different materials, is straightforward, inexpensive, and safe to fabricate, and is easy to use.

Key Words: Mouth shield; Transmission; Dentistry; COVID-19; Airborne; Droplets; Aerosols; Infectious diseases

Core Tip: This letter to the editor presents an innovative mouth shield to increase the protection of the dental team against the water backsplash of aerosols, droplets, and airborne particles during dental procedures.

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TO THE EDITOR

The coronavirus disease (COVID-19) pandemic has spread fear and anxiety across the globe because of its high death toll[1]. Various strategies have been introduced to combat the transmission of COVID-19 and reduce its severity, including the expedited development and approval of vaccines[2]. The risk of transmission of COVID-19 in the dental office has led to specific treatment guidelines and protocols, including the minimal use of aerosol- or droplet-generating procedures[3-6]. However, most dental interventions produce aerosols and droplets, contaminating the surrounding environment and leaving dental personnel at risk of acquiring COVID-19 from infected patients. Although non-emergency dental services were halted at the outset of the pandemic, the long duration of the pandemic has required dental practices to resume their services, but with additional precautions and careful triage of patients [7]. Strict adherence to preventive and protective measures became the mantra for oral care services to maintain an active dental practice at the era of COVID-19[8,9]. The aim of this paper is to introduce an innovative, straightforward, and inexpensive personal protection device that minimizes water backsplash from air-water syringes during cavity washing and drying. The goal was to develop a special mouth shield that should minimize the transmission risk of COVID-19 and other infectious diseases *via* airborne droplets or aerosols in the dental office.

MOUTH SHIELD

The mouth shield attaches to the air-water syringe tip and consists of a transparent shield made from the plastic lid of a conventional, disposable, crystal clear plastic cup. The center of the lid is perforated with a 3.5-mm-diameter twist drill to produce a frictional fit with the tip of an air-water syringe and form a disposable mouth shield (Figures 1A and B). The mouth shield can be positioned to maintain light contact with the patient's lips (Figure 1C). It can be used with most air-water syringes during various dental procedures. Different size lids made from disposable, crystal clear polyethylene terephthalate plastic or polystyrene can be selected to accommodate patients with varying degrees of mouth opening. The front surface of the shield can be relined with a water absorbent liner to capture scattered droplets. The mouth shield can also be easily adjusted forward and backward along the tip (nozzle) of the air-water syringe for convenience (video).

DISCUSSION

The COVID-19 pandemic and the increased risk of infection prompted the authors to develop a cost-effective disposable mouth shield to provide protection against back splashes of aerosols, droplets, and airborne particles during dental treatment. An air-water syringe is essential for dental procedures such as etching, bonding, cavity cleansing, and impression making. Contamination from the aerosol could be a major source of infection[10]. The association between aerosols, droplets, and splatter and the transmission of COVID-19 has been emphasized, and recommendations have been made to reduce their generation during the coronavirus pandemic[4,11-13]. Furthermore, emphasis has been placed on the role of personal protective equipment such as medical masks, protective face shields, and goggles in preventing and minimizing airborne transmission of COVID-19[14,15]. Despite the use of personal protective equipment, transmission of the viral infection is still possible, and additional preventive precautions are advised. For example, while wearing magnifying loops, it is not feasible to wear a face shield, leaving the face of the operator exposed to contamination. The described mouth shield provides additional protection at minimal cost. It is designed to prevent water backsplash out of the oral cavity during mouth/tooth washing and drying, minimizing contamination of the surrounding environment and dental personnel. Being transparent, the shield will allow light to reach the field of operation and

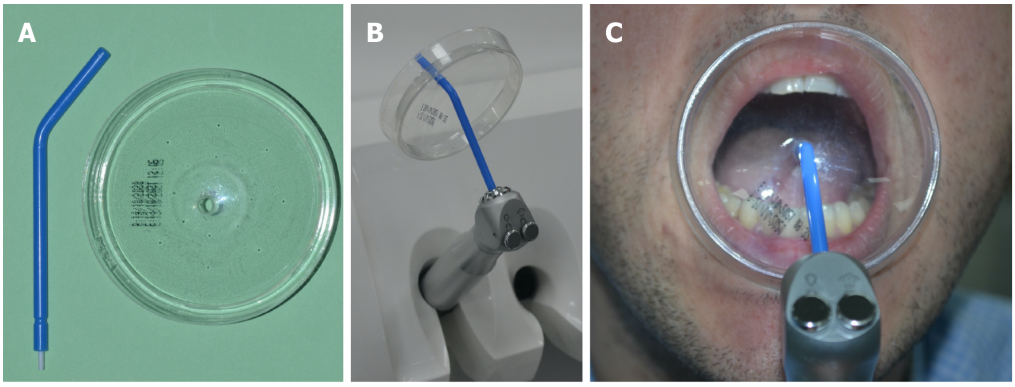

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Figure 1 Crystal clear plastic cup lid mouth shield. A: Traditional, disposable, crystal clear plastic cup lid perforated in the center using a 3.5-mm-diameter twist drill and a disposable air-water syringe tip; B: The air water syringe tip is inserted with a friction fit through the central hole of the plastic cover to form a mouth shield; C: The mouth shield rests lightly on the patient's lips, sealing the mouth during water/air spray.

allow the operator to easily see into the patient's mouth. The described mouth shield has been successfully implemented and evaluated in our dental practice. Nevertheless, the effectiveness of the mouth shield in minimizing the airborne aerosols and droplets spread during dental treatment should be investigated, and its role in protecting against infectious diseases, with a comparison of the load of produced aerosols, droplets and airborne particles with and without this shield, should be examined before this shield can be adopted for global use.

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FOOTNOTES

Author contributions: Dimashkieh MR proposed the topic of the paper; Dimashkieh MR and Nassani MZ prepared the original draft; Talic YF, Alqerban A and Demachkia AM reviewed and revised the original draft; all authors discussed and agreed the final draft.

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