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MINIREVIEWS

Angiotensin-converting enzyme 2 receptors, chronic liver diseases, common medications, and clinical outcomes in coronavirus disease 2019 patients

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Abstract

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus responsible for coronavirus disease 2019 (COVID-19), enters affected cells through the angiotensin-converting enzyme 2 (ACE2) receptor, which is highly expressed in type II alveolar cells, enterocytes, and cholangiocytes. SARS-CoV-2 infection causes fever, dry cough, and breathing difficulty, which can progress to respiratory distress due to interstitial pneumonia, and hepatobiliary injury due to COVID-19 is increasingly recognized. The hepatobiliary injury may be evident at presentation of the disease or develop during the disease progression. The development of more severe clinical outcomes in patients with chronic liver diseases (CLD) with or without cirrhosis infected with SARS-CoV-2 has not been elucidated. Moreover, there is limited data related to common medications that affect the disease severity of COVID-19 patients. Additionally, ACE2 receptor expression of hepatobiliary tissue related to the disease severity also have not been clarified. This review summarized the current situation regarding the clinical outcomes of COVID-19 patients with chronic liver diseases who were treated with common medications. Furthermore, the association between ACE2 receptor expression and disease severity in these patients is discussed.

Key Words: SARS-CoV-2; COVID-19; Hepatobiliary tissue; Angiotensin converting enzyme 2; Chronic liver disease; Common medications; Clinical outcome

Core Tip: With more than 100 million confirmed cases worldwide, hepatobiliary injury has been reported in many coronavirus disease 2019 (COVID-19) patients. The

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Grade B (Very good): 0
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association between COVID-19 and hepatobiliary injury refers to any hepatobiliary damage during disease progression and treatment in COVID-19 patients with or without chronic liver diseases or common medications. Angiotensin-converting enzyme 2 receptor may be a significant factor in hepatobiliary derangement due to its high expression in cholangiocytes, and it is also an entry point of severe acute respiratory syndrome coronaviruses 2. Moreover, drug-induced liver injury and cytokine storm may be an added risk in severe clinical outcomes. Close monitoring of liver function in COVID-19 patients is mandatory.

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INTRODUCTION

Knowledge of the fundamental physiology of angiotensin-converting enzyme 2 (ACE2) has cumulated more than 20 years since its discovery in 2000 and has greatly increased our understanding of the renin-angiotensin system (RAS)[1,2]. The RAS is an essential hormone system with critical roles in blood pressure regulation, vascular biology, nervous system, electrolyte homeostasis, tissue injury, and lipid homeostasis[3,4]. ACE is the key-driven enzyme in classical RAS. On the other hand, the protective RAS is regulated by ACE2 and counterbalances many of the classical deleterious effects of the RAS[5,6]. ACE2 has definite roles ranging from catalytic activities with numerous substrates, as the receptors for severe acute respiratory syndrome coronaviruses (SARS-CoV) and SARS-CoV-2, and as an amino acid transporter[7-10]. ACE2 regulates the RAS by converting angiotensin (Ang) I and II into Ang 1-9 and Ang 1–7, respectively. Clinical and animal studies demonstrated a physiological and pathophysiological aspect of ACE2 in cardiovascular disease (CVD), and activating ACE2 may evoke protective outcomes against hypertension and CVD[11-13].

Since the end of 2019, ACE2 has amassed interest as the cellular receptor of SARS-CoV-2, the causative virus of the coronavirus disease 2019 (COVID-19) pandemic that emerged from Wuhan, China. It has rapidly spread through China, crossed the global borders of 221 countries, and infected 101529722 people, with 2186606 deaths resulting in a 2.15% mortality rate[14]. The clinical manifestations of COVID-19 patients include cough, fever, sore throat, diarrhea, and loss of sense of taste or smell. More than 80% of infected patients have mild symptoms, 14% have severe symptoms, and 5% have a critical illness. Older patients and those with medical co-morbidities are at risk of a severe disease course[15]. Previous studies demonstrated liver damage in nearly 60% of patients suffering from SARS. They also found SARS-CoV virus particles in the hepatocytes of patients[16]. Moreover, SARS-CoV-2 is associated with hepatic dysfunction ranging from 14% to 53% with abnormal levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) without known liver disease[17-19]. Patients with severe or critical outcomes showed higher frequency and degree of liver dysfunction, while in milder patients, the liver injury was transient[20]. Liver injury in COVID-19 patients included psychological stress, systemic inflammation response, drug toxicity, the progression of pre-existing chronic liver diseases (CLD), and other factors[21]. Hence, three possible scenarios have been postulated. Firstly, patients with CLD and pre-existing co-morbidity diseases may be more prone to the severe clinical outcomes of COVID-19, including oxygen desaturation and hypoxemia due to severe pneumonia or the cytokine storm. Secondly, liver enzyme abnormalities are the consequence of drug toxicity. Thirdly, SARS-CoV-2 directly or indirectly causes liver injury[22-24]. Although ACE2 receptors are abundantly present in type 2 alveolar cells, they are also expressed in the gastrointestinal tract, vascular endothelium, hepatocytes, and cholangiocytes and may be the significant factors in disease severity. This review will clarify the relationship between CLD, common medications, and the expression of ACE2 with the clinical outcomes in COVID-19 patients.

ACE2 RECEPTOR

Physiology of ACE2 receptor

ACE2 receptor resembles the ACE receptor and plays a crucial role in the renin-angiotensin-aldosterone system (RAAS), including blood pressure control and electrolyte homeostasis. The liver produced angiotensinogen, which is cleaved by renin from the kidney, results in Ang I. After that, ACE catalyzes the conversion of Ang I to Ang II. Ang II is the significant active RAAS portion and exerts its effects *via* Ang II type 1 receptor. Furthermore, Ang II's main effects include vasoconstriction, renal sodium reabsorption, potassium excretion, aldosterone synthesis, blood pressure elevation, and induction of pro-inflammatory and pro-fibrotic pathways. ACE2 splits Ang II to Ang (1-7) and Ang I to Ang (1-9). Furthermore, Ang (1-9) is cleaved by ACE to Ang (1-7). Ang (1-7) exerts vasodilatation, anti-inflammatory, and anti-fibrotic effects through the Mas receptor to counterbalance Ang II's action. Notably, ACE2 functionally counteracts the physiological role of ACE and creates the tissue balance of ACE and ACE2, which determines the pro-inflammatory, pro-fibrotic, or anti-inflammatory and anti-fibrotic pathways[25,26] (Figure 1). The common drugs prescribed for RAAS blockade in several disease conditions can affect this balance. Moreover, many dietary factors (high sodium, high fat, and high fructose intake) can also shift the ACE/ACE2 balance towards pro-inflammatory and pro-fibrotic[27-29].

Expression of ACE2 receptor in hepatobiliary tissue

In 2004, Hamming *et al*[30] investigated the immuno-localization of ACE2 in 93 human specimens and found that ACE2 was present in endothelial cells from small arteries, large arteries, and veins in the studied tissues. Marked ACE2 immuno-staining was found in type I and typed II alveolar epithelial cells in normal lungs. ACE2 was abundantly demonstrated in enterocytes of all small intestine but not in the enterocytes of the large intestine. ACE2 was not found in lymphoid tissues and hepatocytes. Recently, Xu *et al*[31] investigated ACE2 expression in the oral cavity mucosa and various organs, including the intestine, kidney, stomach, bile duct, liver, lungs, thyroid, esophagus, bladder, breasts, uterus, and prostate. They found that ACE2 could be expressed in various organs. The mean expression of ACE2 in the liver, bile duct, and lungs was 6.86 ± 1.35, 7.23 ± 1.16, 5.83 ± 0.71, respectively. This result demonstrated that the expression of ACE2 in the lungs and the liver was not different. Moreover, Zhao *et al*[32] identified ACE2 expression sparsely in cholangiocytes of human liver ductal organoids cells. Anti-ACE2 immuno-staining further confirmed the presence of ACE2 receptors on those cells. Furthermore, Li *et al*[33] explored the underlying liver injury mechanism by profiling ACE2 expression with CLD expression data. They found that the liver tissues with chronic diseases, such as cirrhosis, non-alcoholic steatohepatitis, simple steatosis, and dysplasia, could express higher levels of ACE2 than normal liver tissues.

The relationship between common medications and ACE2 expression

Sinha *et al*[34] performed *in vitro* and *in vivo* studies to identify the clinically approved drugs that could modify ACE2 expression. They found that ACE inhibitors (ACEIs) but not angiotensin II type-I receptor blockers (ARBs) tend to upregulate ACE2 expression, and anti-adrenergic drugs other than alpha/beta-blockers tend to down-regulate ACE2 expression. Moreover, calcium channel blockers (CCBs) do not significantly change ACE2 expression, consistent with the finding that they do not act on the RAAS. This evidence provides preliminary *in vitro* support for the use of CCBs as an alternative to ACEIs in COVID-19 patients with hypertension. They also studied the 13 approved anti-diabetic drugs related to ACE2 expression, and they could not demonstrate that the drugs significantly altered ACE2 expression. Surprisingly, they reported that intravenous dexamethasone injection could increase ACE2 expression. They also demonstrated the effect of vancomycin, which increased an ACE2 expression. Saheb SharifAskari *et al*[35] studied the effect of common medications on the expression of ACE2 receptors in human primary hepatocytes. They found that the top three drugs that increased ACE2 expression were penicillamine, ethambutol, and vitamin A. The top five drugs that decreased ACE2 expression were colchicine, acetaminophen, sulindac, diazepam, and nimesulide. The top five drugs that did not change ACE2 expression were ibuprofen, lornoxicam, mefenamic acid, meloxicam, and methyltestosterone.

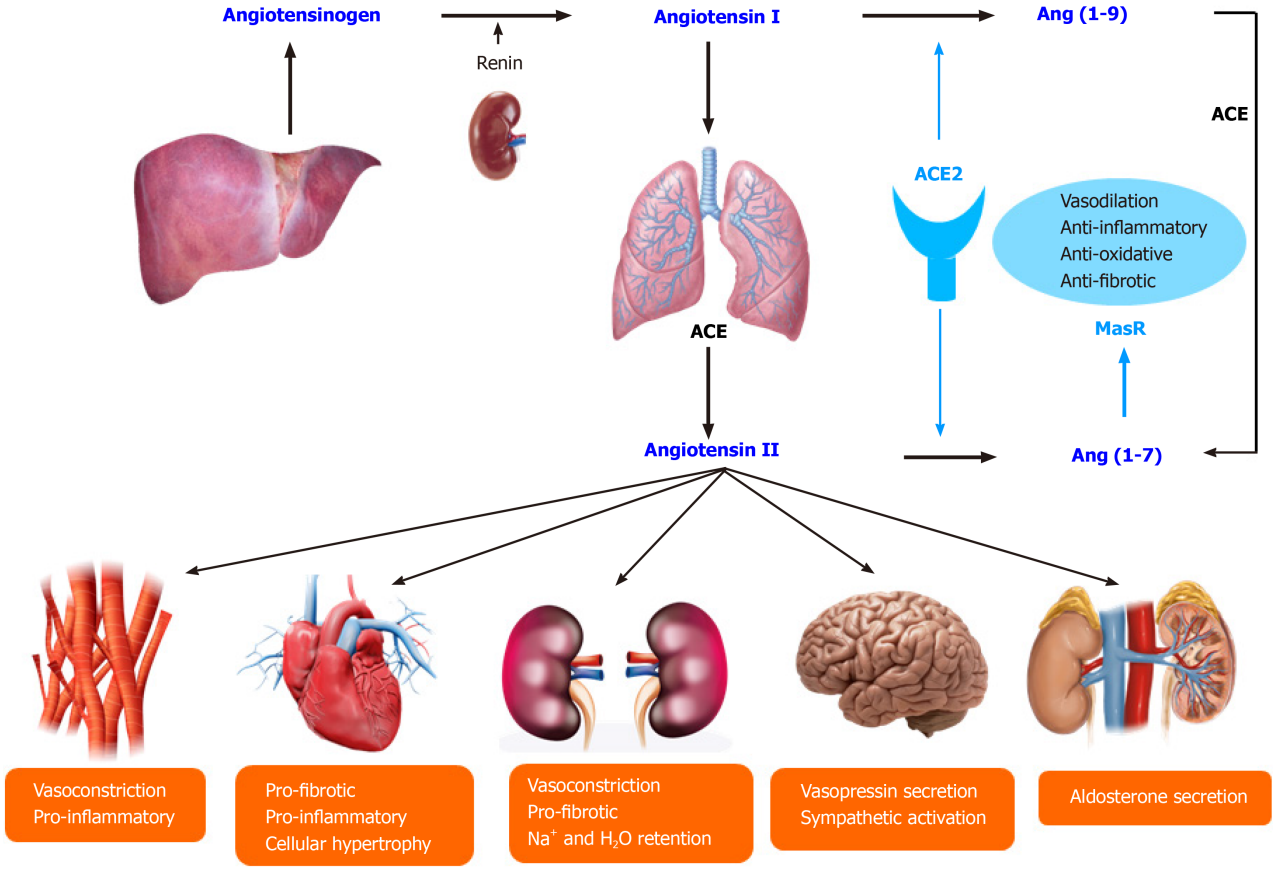

Figure 1 The renin-angiotensin-aldosterone system and the physiology of angiotensin-converting enzyme 2. ACE: Angiotensin-converting enzyme.

COVID-19 AND HEPATOBILIARY INJURY

Laboratory evidence of hepatobiliary injury

Previous studies have shown that nearly 60% of SARS patients developed a hepatobiliary injury and that SARS-CoV antigens were detected in liver tissues by reverse transcription-polymerase chain reaction[36,37]. Hepatobiliary injury in COVID-19 patients was also demonstrated by abnormal transaminase levels linked to the disease severity and the clinical outcome. Abnormal liver enzymes in COVID-19 patients were first reported by Chen *et al*[38]. They analyzed data of 99 COVID-19 patients from Wuhan and found that 43 cases (43.4%) had elevated ALT, AST, and lactic dehydrogenase. Most of them had a mild elevation of AST and ALT, and only one patient had very high ALT levels of 7590 U/L and AST levels of 1445 U/L. Recently, Kulkarni *et al*[39] conducted a systematic review with meta-analysis to evaluate the liver manifestations and clinical outcomes in 20874 COVID-19 patients. They found that the pooled incidence of elevated AST and ALT in COVID-19 was 23.1% (19.3%-27.3%) at initial presentation. Moreover, 24.4% (13.5%-40%) of the patients developed elevated AST and ALT during the illness. They also reported the prevalence of underlying CLD as 3.6% among the 15407 COVID-19 patients. The pooled incidence of drug-induced hepatobiliary injury was 25.4% (14.2%-41.4%). They found that the development of severe COVID-19 in CLD patients had an odds ratio (OR) of 0.81 [95% confidence interval (CI): 0.31-2.09] compared with non-CLD patients. Furthermore, COVID-19 patients with elevated AST and ALT had increased risk of mortality (OR = 3.46, 95%CI: 2.42-4.95, $P < 0.001$) and severe disease (OR = 2.87, 95%CI: 2.29-3.6, $P < 0.001$) when compared with the patients without elevated AST and ALT.

Recently, Del Zompo *et al*[40] conducted a systematic review with meta-analysis to elucidate the prevalence of hepatobiliary injury in 20724 COVID-19 patients with or without pre-existing CLD. They found that the pooled prevalence of abnormal liver function tests (LFTs) on admission was 46.9% [AST 26.5%, ALT 22.8%, gamma-glutamyl transferase (GGT) 22.5%, alkaline phosphatase (ALP) 5.7%, and total bilirubin (tBIL) 8.0%]. The elevation of ALT, AST, and tBIL were independent predictors of disease severity and in-hospital mortality. Wong *et al*[41] conducted

another systematic review with meta-analysis to evaluate the prevalence and degree of liver injury in 5961 severe and non-severe COVID-19. They found that the OR for elevated ALT was 2.5, AST was 3.4, hyperbilirubinemia was 1.7, and hypoalbuminemia was 7.1, which were higher in critical COVID-19. They concluded that hepatobiliary injury is more common in COVID-19 patients with severe clinical outcomes than in COVID-19 patients with non-severe clinical outcomes.

Mao *et al*[42] conducted another meta-analysis to evaluate the prevalence and prognosis of gastrointestinal symptoms and hepatobiliary injury in 6686 patients with COVID-19. They found that the pooled prevalence of liver co-morbidities was 3%, including chronic hepatitis and liver cirrhosis. The pooled prevalence of liver injury from 12 studies (n = 1267) was 19%. The prevalence of elevated ALT was 18%, AST was 21%, tBIL was 6%, and decreased albumin was 6%. They also reported a higher risk of abnormal LFT in patients with severe COVID-19 than those with the non-severe disease.

Kumar-M *et al*[43] conducted another meta-analysis to evaluate the overall prevalence, stratified prevalence based on severity, estimated risk ratio (RR), and estimated standardized mean difference (SMD) of liver function parameters in severe compared to non-severe COVID-19 patients with a total number of 28659 subjects. They found that the most frequent abnormalities were hypoalbuminemia (61.27%), elevated GGT = 27.94%, elevated ALT = 23.28%, and elevated AST = 23.41%. Furthermore, the relative risk (RR) of these abnormalities was higher in the patients with severe COVID-19 when compared to non-severe disease (hypoalbuminemia RR = 2.65; GGT RR = 2.31; AST RR = 2.30; and ALT RR = 1.76). The pooled prevalence and RR of CLD as a pre-existing co-morbidity were 2.64% and 1.69%, respectively. They concluded that the most frequent hepatobiliary injury was hypoalbuminemia followed by elevated GGT, elevated AST, and elevated ALT, which were more common in severe COVID-19 patients.

Youssef *et al*[44] conducted a meta-analysis of 3428 COVID-19 patients to elucidate the relationship between hepatobiliary injuries and the severity of COVID-19 disease. They found that the patients who had severe presentations of COVID-19 had hypoalbuminemia (SMD = 0.68), elevated AST (SMD = 0.36), elevated ALT (SMD = 0.44), and elevated tBIL (SMD = 0.40). They also reported that severe COVID-19 patients had a higher OR of developing acute hepatobiliary injury (OR = 1.93). They concluded that hepatobiliary injury was related to a critical outcome of COVID-19 patients. Close monitoring of the development of liver dysfunction is beneficial in early warning of unfavorable outcomes.

Wang *et al*[45] conducted a meta-analysis to evaluate the association of liver injury and gastrointestinal symptoms (GIS) with the progression of COVID-19 in 3024 patients. They found that 53% of patients had a hepatobiliary injury, and the degree of hepatobiliary damage was associated with disease severity. The prevalence of GIS was relatively low and was not associated with disease progression, with diarrhea of 9.1%, nausea/vomiting of 5.2%, and abdominal pain of 3.5%.

Wu *et al*[46] conducted a meta-analysis to explore the probable clinical severity and mortality of COVID-19 patients and their liver dysfunction in 3722 COVID-19 patients. They found a significant connection between hepatobiliary dysfunction and mortality in COVID-19 patients with a pooled OR of 1.98. There was a significant association between elevated AST and severity of COVID-19 with a pooled OR of 4.48 and a pooled weighted mean difference of 3.35. They also found a significant difference between elevated tBIL and severe COVID-19 (pooled OR = 1.91 and pooled weighted mean difference = 1.18). They concluded that the mortality and severity of COVID-19 patients are significantly associated with hepatobiliary dysfunction.

Samidoust *et al*[47] conducted a meta-analysis study to investigate the incidence of liver injury among 4191 COVID-19 patients. They found that the pooled prevalence of liver injury was 19.5%. They concluded that hepatobiliary system is the most frequently damaged outside of the respiratory system. Wu *et al*[48] conducted the meta-analysis to explore the incidence, risk factors, and prognosis of abnormal liver biochemical tests in 7228 COVID-19 patients. They found that the pooled prevalence of any abnormal liver biochemistry parameters on admission and during hospitalization was 27.2% and 36%, respectively. The most common prevalence was hypoalbuminemia followed by GGT, AST, ALT, tBIL, and ALP (39.8%, 35.8%, 21.8%, 20.4%, 8.8%, and 4.7%). Moreover, severe or critical patients had a significantly higher pooled incidence of abnormal liver biochemistry parameters on admission than mild or moderate patients. Non-survival patients also had a significantly higher incidence of abnormal liver biochemical indicators than survival patients (RR = 1.34). They concluded that abnormal liver biochemical tests are common and are closely related to the severity and prognosis of COVID-19 patients.

Mantovani *et al*[49] conducted the meta-analysis to assess the overall prevalence of CLD among 2034 COVID-19 patients. They found that the overall prevalence of CLD at baseline was 3%, and patients with severe COVID-19 disease had relevant increases of liver enzymes and coagulation profile due to the innate immune response against the SAR-CoV-2 virus. Sultan *et al*[50] conducted the meta-analysis to summarize international data on the gastrointestinal (GI) and liver manifestations of SAR-CoV-2 infection and treatment in 10890 COVID-19 patients. They found that elevated AST, elevated ALT, and elevated tBIL are observed in approximately 15%-20% of COVID-19 patients. These findings inform that the clinician should perform a careful evaluation of patients with new-onset GI symptoms for classic and atypical symptoms of COVID-19. All hospitalized COVID-19 patients may benefit from liver enzyme monitoring, particularly in drug treatment with known hepatotoxic potential.

Pathological finding of hepatobiliary injury

Xu *et al*[51] reported the first post-mortem findings of a patient who succumbed to severe COVID-19. They found that the liver histology showed moderate microvesicular steatosis and mild inflammatory infiltrates in the hepatic lobule and portal tract. They do not know whether these changes were from the direct viral injury or drug toxicity. Wichmann *et al*[52] conducted a prospective cohort study to perform the autopsies of 12 consecutive COVID-19 deaths, including post-mortem computed tomography and histopathologic and virologic analyses. The median patient age was 73 years (52 to 87 years), 75% of patients were male, and death occurred in the hospital (n = 10) or outpatient department (n = 2). They did not report the histopathology of the hepatobiliary system; however, they could demonstrate the detection of SARS-CoV-2 ribonucleic acid in the lungs of 12 patients (1.2×10^4 to 9×10^9 copies/mL) and the pharynx of nine patients. In five of these patients, viral ribonucleic acid was also detected in the heart, liver, and kidney. They concluded that SARS-CoV-2 might spread *via* the bloodstream and infect other organs, including the hepatobiliary system. Tian *et al*[53] performed post-mortem needle core biopsies of lung, liver, and heart in four patients who died of COVID-19 pneumonia. They found that the liver histopathology showed mild lobular infiltration by small lymphocytes, centrilobular sinusoidal dilatation, focal macrovesicular steatosis, and patchy hepatic necrosis in the periportal and centrilobular areas. Tabary *et al*[54] reviewed multiple organs, including lung, GI tract, liver, kidney, skin, heart, blood, spleen, lymph nodes, brain, blood vessels, and placenta, in COVID-19-related pathological alterations. The liver found hepatocyte degeneration with lobular focal necrosis, congestion of hepatic sinuses with microthrombus, fibrosis of portal tract, the proliferation of portal vein branches, mononuclear leukocyte, and neutrophil infiltration within the portal area and moderate microvascular steatosis. Yao *et al*[55] conducted another histopathology of the hepatobiliary system. They found that the liver exhibits mild sinusoidal dilation, with mildly increased small lymphocytes infiltration in sinusoidal spaces. Mild to moderate steatosis and multifocal hepatic necrosis have been reported. These findings confirmed that the hepatocellular injury in COVID-19 patients should be considered as a significant factor in disease severity.

CLD AND CLINICAL OUTCOME

The COVID-19 patients with pre-existing CLD usually face a relatively high risk of poor clinical outcomes. Li *et al*[33] established that patients with CVDs could express higher ACE2 expression than those without heart diseases. Furthermore, ACE2 was upregulated in patients with type 2 diabetes (T2D) compared to the individuals without T2D. For CLD such as cirrhosis, non-alcoholic steatohepatitis, and simple steatosis, ACE2 could express higher levels than normal liver tissues. The upregulation of ACE2 expression in patients with CLD may result in greater susceptibility to SARS-CoV-2 infection of hepatobiliary tissues. Sarin *et al*[56] conducted The APASL COVID-19 Liver Injury Spectrum Study (APCOLIS Study) to evaluate the liver injury patterns of SARS-CoV-2 in 185 CLD patients without cirrhosis compared with 43 CLD patients with cirrhosis. They found that pre-existing CLD, like metabolic associate fatty liver disease, obesity, and diabetes, was present in nearly 80% of the patients. Moreover, SARS-CoV-2 infection produces acute liver injury in 43% of CLD patients without cirrhosis. Nearly half of decompensated cirrhosis patients develop liver-related complications, which were more severe and had higher mortality. The liver injury pattern in CLD patients was mostly a hepatocellular injury. Notably, elevated serum ALP and elevated GGT were detected, indicating virus-related injury to hepatobiliary

tissue due to the overexpression of ACE2 on cholangiocytes. They also found acute, chronic liver failure (ACLF) or acute decompensation in 20% of the cirrhotic patients, which indicated that SARS-CoV-2, a non-hepatotropic virus, can directly precipitate a severe hepatic injury to cause liver failure in cirrhotic patients. They concluded that pre-existing CLD is an added risk in severe COVID-19 patients. Liver-related complications, overall complications, and clinical outcomes correlated with the existing hepatic reserve. Moreover, acute liver injury is more severe and more progressive with higher mortality in COVID-19 patients with decompensated cirrhosis.

Marjot *et al*[57] conducted an international registry study to evaluate the impact of COVID-19 on patients with pre-existing CLD. They recruited 745 patients with CLD who were infected with SARS-CoV-2 (386 with cirrhosis and 359 without cirrhosis) and compared them to non-CLD patients with SARS-CoV-2 infection. They found that the mortality rate was 32% in COVID-19 patients with cirrhosis compared to 8% in those without cirrhosis. Mortality in cirrhosis patients increased according to Child-Pugh Class [A (19%), B (35%), and C (51%)] and 71% of death was an acute respiratory distress syndrome. Compared to COVID-19 patients without CLD (n = 620), the propensity-score-matched analysis revealed a significant increase in mortality in those with Child-Pugh B cirrhosis (+ 20.0%) and Child-Pugh C cirrhosis (+ 38.1%). Acute hepatic decompensation developed in 46% of cirrhosis patients, of whom 21% had no respiratory symptoms. Half of those with hepatic decompensation had ACLF. They concluded that baseline liver disease and alcohol-related liver disease are independent risk factors for death from COVID-19. Another group of investigators from Korea conducted a multicenter study to evaluate the clinical outcomes in 1005 COVID-19 patients related to pre-existing CLD and the predictors of disease severity and mortality. They found that liver cirrhosis was more common in COVID-19 patients with severe pneumonia than in non-severe pneumonia (4.5% *vs* 0.9%). The overall survival rate significantly decreased in COVID-19 patients with liver cirrhosis than in those without liver cirrhosis. The presence of liver cirrhosis was found to be an independent predictor of severe clinical outcome. They suggested that more robust personal protection and more intensive treatment for COVID-19 with pre-existing CLD should be highly recommended[58].

Del Zompo *et al*[40] conducted the meta-analysis to elucidate the prevalence of hepatobiliary injury in COVID-19 patients with or without pre-existing CLD. They explored 36 studies, including 20724 patients with SARS-CoV-2 infection, and found that LFTs alterations were reported in up to 47% of unselected patients with COVID-19 and were associated with severe clinical outcomes or in-hospital mortality. COVID-19 was associated with a high risk of liver decompensation or mortality. Váncsa *et al*[59] conducted the meta-analysis to evaluate the prognostic value of on-admission LFTs and pre-existing CLD on the clinical course of COVID-19. They evaluated 50 studies with 17205 COVID-19 patients. They reported that the decreased platelet count, elevated ALT, elevated AST, increased C-reactive protein, and the presence of acute or CLDs at the time of admission could predict severe clinical outcomes of COVID-19 patients. Significantly, the pre-existing CLD or acute liver injury combined with SARS-CoV-2 infection was an important factor in predicting mortality rate.

COMMON MEDICATIONS TREATMENT AND CLINICAL OUTCOME IN COVID-19 PATIENTS

Several publications reviewed the role of RAS inhibitors in COVID-19 patients and found that there is no definitive evidence indicating harmful effects of RAS inhibitors. Because ACE and ACE2 are different enzymes, ACEIs do not inhibit ACE2, making this class' harmful effect unlikely[60-62]. Other common anti-hypertensive drugs are ARBs, which have been shown to upregulate ACE2 in animal studies, but these findings do not translate into clinical observations related to COVID-19[63]. Drager *et al*[64] summarized that the available clinical evidence points to a neutral or even beneficial effect on clinical outcomes in COVID-19 patients who received ACEIs or ARBs. Luo *et al*[65] conducted a retrospective analysis to compare the outcome of metformin users and non-users in 283 hospitalized COVID-19 patients with diabetes (104 used metformin, and 179 did not use metformin). They found that in-hospital mortality was significantly lower in the metformin group [3/104 (2.9%) *vs* 22/179 (12.3%), P = 0.01]. They concluded that metformin might offer benefits in COVID-19 patients. However, they did not mention the relationship between metformin and hepatobiliary injury in their study. Treatment of common co-morbidities such as cardiovascular, hepatobiliary, and metabolic disorders often requires continuous use

of several medications, which may result in an additive increase in the expression of ACE2. Furthermore, the combined effect of chronic use of these medications could affect liver susceptibility in COVID-19 patients. Although the increased risk of developing severe clinical outcomes in COVID-19 patients should not be the direct effect of common medications, we should be vigilant about the possible effects of those medications.

CONCLUSION

Several factors have been associated with the alteration of ACE2 expression and COVID-19 severity and progression. Although ACE2 is widely expressed in various human tissues and most of its determinants have been well recognized, ACE2-expressing organs do not equally participate in COVID-19 pathophysiology, implicating that other factors are involved orchestrating cellular infection resulting in several organs injury. Abnormal LFTs are reported in up to half of the patients with COVID-19 infection. The disease severity, pre-existing CLD, and some common medications presented risks for hepatobiliary injury in COVID-19 patients. It has been demonstrated that SARS-CoV-2 may directly bind to ACE2 positive cholangiocytes and cause severe hepatic injury. However, pre-existing CLD and some common medications could also upregulate ACE2 expression in the hepatobiliary tissues and cause more severe clinical outcomes in COVID-19 patients. Furthermore, other contributing mechanisms such as drug-induced liver injury, activation of the immune system, and cytokine storm may be the other contributing factors in severe clinical outcomes.

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MINIREVIEWS

Impact of COVID-19 in patients with lymphoid malignancies

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Abstract

The first cases of coronavirus disease 2019 (COVID-19) were detected in Wuhan, China, in December 2019. Since this time a concerted global effort of research and observational data gathering has meant that a great deal has been learnt about the impact of COVID-19 in patients with lymphoid malignancies. Approximately one-third of patients with lymphoid malignancies who acquire COVID-19 and have it severely enough to require hospital assessment will die from this infection. Major risk factors for a poor outcome are age and co-morbidities, but when these are taken into account lymphoma patients have a slightly greater than 2-fold increased risk compared to the general population. Notably, despite early concerns regarding the particular vulnerability of lymphoma patients due to the immunosuppressive effects of therapy, active treatment, including B-cell depleting agents such as rituximab, do not appear to be associated with an increased risk of a poorer outcome. Indeed, some treatments such as ibrutinib may be beneficial due to their modulation of the potential fatal hyperinflammatory phase of infection. There are risks associated with hemopoietic stem cell transplantation, but the collective experience is that these can be minimized by preventive strategies and that the majority of transplant recipients with COVID-19 infection will survive. Many questions remain including those regarding the outcome of COVID-19 infection in the rarer lymphoid malignancies and the efficacy of COVID-19 vaccines in lymphoma patients. This review aims to discuss these issues and present a summary of the current knowledge of the impact of COVID-19 in lymphoid malignancies.

Key Words: COVID-19; Lymphoma; Leukemia; Chemoimmunotherapy; Hemopoietic stem cell transplantation; Vaccination

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Core Tip: Patients with lymphoid malignancies who have coronavirus disease 2019 (COVID-19) severely enough to require hospital assessment have an approximately one-third chance of dying from the infection, representing a slightly greater than 2-fold increased risk compared to the general population. Despite initial concerns, treatment for lymphoma is not associated with increased risk for poor outcome. Current evidence for the efficacy of COVID-19 vaccines in patients with lymphoid malignancies is extremely limited, so it will be crucial to conduct studies to address this issue over the coming months.

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INTRODUCTION

The first cases of coronavirus disease 2019 (COVID-19) were detected in Wuhan, China, in December 2019. The disease, caused by a novel RNA beta coronavirus, severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), was initially reported as predominantly causing a pulmonary syndrome, typified by fevers in combination with breathlessness and cough[1]. However, it is now appreciated that COVID-19 can cause a wide range of symptoms of variable severity, including fatigue, myalgia, headache, anosmia, pharyngitis, coryza, nausea and diarrhoea[2]. Since initial detection of the virus, more than 130 million cases of COVID-19 have been confirmed worldwide, with more than 2.8 million deaths[3]. Initial reports from China have indicated that COVID-19 has an overall mortality rate of 1.4%. However, the prognosis varies widely between groups, with those people over the age of 60 years and those with underlying conditions, including hypertension, diabetes, cardiovascular disease, chronic respiratory disease and cancer, at a significantly higher risk for severe disease and death[4].

There has been a great deal of concern that patients with lymphoid malignancies such as lymphomas and lymphoid leukemias would be at particular risk from COVID-19. The initial reports from China showed that patients with cancer were over-represented among individuals who developed severe COVID-19 after contracting the virus[5]. Patients with lymphoid malignancies could be expected to be at increased risk of adverse outcomes from this viral infection, both due to being immuno-compromised as a consequence of the underlying cancer, and due to the myelosuppressive and lymphodepleting effects of therapy. A number of retrospective studies have reported outcomes of patients with lymphoid malignancies who became infected with SARS-CoV-2 during or shortly after treatment[6-21]. These were pooled into a large meta-analysis of 3377 patients with hematological malignancies who developed COVID-19 with a primary outcome of risk of death[22]. Among all blood cancers the overall risk of death was 34%, rising to 39% when combining data for hospitalized patients. Within this the pooled risk of death was also calculated by hematologic malignancy subtype with lymphomas including/excluding chronic lymphocytic leukemia (CLL) having a risk of death of 32%, with CLL specifically having a risk of 31%. This was comparable to myeloproliferative neoplasms (34%) and plasma cell dyscrasias (33%), but somewhat less than acute leukemias (41%) and acquired bone marrow failure syndromes (53%). Notably the primary risk factor for COVID-19 mortality was age with patients aged 60 years and older having a significantly higher risk of death than patients under 60 years. While these "headline" figures are rather high, one of the major limitations of these retrospective studies was that almost all of them focused on patients who were either assessed in hospital, or were actually hospitalized for their COVID-19. Invariably, these patients had more severe infections than those who remained at home, who were not necessarily detected and included in these studies, making these mortality statistics an over-estimation. Ascertaining the true mortality rates remains challenging and governments around the world continue to advise patients with mild COVID-19 symptoms to self-isolate at home. At the time of our own study the United Kingdom was focused on hospital-based testing for suspected COVID-19, representing a comparable group of patients to the meta-

analysis[23]. This allowed an estimation of a crude case fatality rate of 14% suggesting that blood cancer patients have a 2-2.5 -fold greater risk of dying from COVID-19 than the general population. The largest single study to date also likely has the best estimate of true population mortality risk from COVID-19 for hematological cancer patients as they used population-based data from a countrywide Ministry of Health database[18]. This reported a risk of death 14%, which was twice that of a control population in their study (7%) and was comparable to the estimated risk of death of 13% in patients with all cancers[24]. A further study from Italy of 536 patients with hematologic malignancies and COVID-19 reported a mortality rate 37%, with a standardized mortality ratio for of 2.04 increased risk when compared with the impact of COVID-19 in the general Italian population[13]. Taken together, these studies have fairly consistently demonstrated that approximately one-third of patients with hematological malignancies who acquire COVID-19 and have it severely enough to require hospital assessment and/or admission will die from this infection. The major risk factors are age and co-morbidities, but when these are taken into account patients with blood cancers have a slightly greater than 2-fold increased risk compared to the general population.

IMPACT OF COVID-19 BY LYMPHOMA SUBTYPE

Many of the larger studies have pooled all patients with hematological cancers together. While this is useful, clearly there is very significant heterogeneity within this group of diseases, in respect of pathophysiology, clinical characteristics, and the type and intensity of treatment. Therefore, studies which have included patients with a single disease/disease group can give more "granularity" and aid physicians in informing their patents. At the time of writing, the lymphoid malignancy with the most data in this regard is CLL. Patients with this leukemia could be hypothesized to be particularly vulnerable to SARS-CoV-2 infection. This is due to the fact that CLL is frequently accompanied by an immunodeficiency which can be further aggravated by therapy, and also that it typically effects older adults (median age at diagnosis 70 years) who are higher risk due to their age[25,26]. A number of studies have now looked at the impact of COVID-19 in CLL patients specifically. Perhaps, due to the geography of the pandemic one of the first reports was from an Italian group who assessed 47 symptomatic CLL patients were found to be positive for COVID-19[27]. Of the 46 evaluable patients, 14 died, equating to a morality rate of 30.4%. The median age of these patients was 75 years, meaning that the mortality rate of this group was only a little higher than the mortality rate of 25.5% in 70-79-year-olds in the general Italian population at the same time. The European Research Initiative on CLL group reported outcomes of 190 CLL patients who presented in the first wave of the pandemic. 151 (79%) presented with severe COVID-19 (requiring oxygen and/or intensive care admission) which was associated with more advanced age (≥ 65 years) with a mortality rate of 36.4%[15]. Mato *et al*[12] reported data from a further international (predominantly United States) multi-center cohort of 198 patients. This again revealed a relatively high rate of severe disease and hospital admissions with an overall case fatality rate of 33%. This rose to 37% in those requiring admission, a remarkably similar figure to the other study. Across these two major studies the main risk factors were mainly those already known for COVID-19 itself: age and co-morbidities. Interestingly, hypogammaglobulinemia, a marker of the CLL-associated immunodeficiency, did not impact upon the outcome. It could be hypothesized that the immune defect associated with this defect could be a "double-edged" sword. On one hand, a weakened immune system may not be as capable of eliminating SARS-CoV-2, yet on the other, it might help to prevent a fatal immune and inflammatory over-reaction[28].

They have been a few reports of the outcomes of COVID-19 more specifically in patients with lymphoma. A study by Lamure *et al*[29] investigated the outcomes of 89 patients, the majority of whom had recently treated (within the last year) B-cell non-Hodgkin lymphoma. With a median follow-up of 33 d from admission, 30-d overall survival was 71%, with age ≥ 70 years and relapsed/refractory lymphoma being risk factors for a poorer outcome in a multivariate analysis. They did not see any differences in outcomes of patients with B-cell *vs* T-cell lymphomas, but they only included 7 patients in the latter group. Recent bendamustine treatment was also identified as a potential risk factor. However, the numbers of patients were few and this characteristic was strongly associated with (and probably confounded by) relapsed/refractory lymphoma. Notably they concluded that survival of patients younger than 70 years without relapsed/refractory lymphoma was comparable to that

of the general population[29]. A further Spanish study reported on 177 patients, 89% of who had non-Hodgkin lymphoma. The overall mortality rate was 34.5%, with age > 70 years, heart disease, chronic kidney disease, CURB-65 score ≥ 2 and active disease significantly increasing the risk of death in a multivariate analysis. Interestingly they did also note that the persistence of a positive polymerase chain reaction for SARS-CoV-2 after week 6 was significantly associated with mortality, suggesting that longer term viral suppression is an important component of recovery[30].

Not unexpectantly current published data is limited to small case series and case reports when it comes to the rarer forms of lymphoma. A Parisian study reported outcomes for 13 patients with primary central nervous system lymphoma. The mortality rate was 23% in this group, 11 (85%) of whom were undergoing chemotherapy at the time of infection. Two additional patients (15%) required mechanical ventilation, but two patients (15%) had no COVID-19 symptoms. A medical history of diabetes mellitus was more common in patients with severe disease. Chemotherapy was resumed after COVID-19 recovery in nine patients (69%) after a median delay of 16 d with no unusual chemotherapy complications nor incidents of SARS-CoV-2 reactivation[31]. Gonzaga *et al*[32] reported on the outcome of 2 patients with Sezary syndrome who acquired COVID-19. Unfortunately, both patients died, one attributable to COVID-19 and the other due to progressive disease. In contrast another patient who was receiving treatment for lymphoma type adult T-cell leukemia-lymphoma recovered after developing severe COVID-19 pneumonia with favipiravir therapy. Interestingly, there have also been a few reports of COVID-19 being beneficial to lymphoma patients, presumably due to an "immunostimulatory effect". Challenor and Tucker[33] reported the case of a 61-year-old man who went into remission after SARS-CoV-2 infection without treatment. Sollini *et al*[34] also report a case of a patient with follicular lymphoma, who having achieved a partial remission after bendamustine-based therapy, went onto achieve a complete remission after asymptomatic COVID-19. In addition, Pasin *et al*[35] report an interesting case of a patient with natural killer (NK)/T-cell lymphoma who having been refractory to previous immuno-chemotherapy, subsequently developed a transient remission at the time if SARS-CoV-2 infection. As NK cells express angiotensin converting enzyme 2, the binding site for this virus, they hypothesize that a direct oncolytic effect of the virus combined with production of proinflammatory cytokines led to NK-cell apoptosis, something seen with other RNA viruses. Clearly, more data needs to be collected on these and other types of lymphoid malignancies, something that will almost certainly occur as the pandemic progresses.

INTERACTION OF COVID-19 AND TREATMENT OF LYMPHOMA

While a large part of this involves the management of bacterial infections, particularly in the context of concurrent neutropenia, infection with and re-activation of viruses are also a feature of the clinical course of many lymphoma patients on treatment. Prolonged symptoms from seasonal "flu" and "cold" viruses and reactivation of viruses such as hepatitis B and varicella zoster are common complications of treatment, particularly after depletion of the B-cell compartment with anti-CD20 monoclonal antibodies such as rituximab. Given that most effective lymphoma therapies are also lymphodepleting it could be expected that anti-lymphoma drugs would compromise the normal immune response to SARS-CoV-2 leading to prolonged and more severe infection. However, even in the early stages of the pandemic it was clear that this was not so straightforward. The infection typically begins with relatively mild symptoms, which if the infection is not controlled, then can become more severe at around day 10 associated with a cytokine-induced inflammatory storm as the "adaptive" immune response takes off. Therefore, it could also be hypothesized that the immunosuppressive effect of many lymphoma treatments could actually be beneficial at this stage by limiting this hyperinflammation, thereby avoiding severe pneumonitis and thrombotic sequelae. In light of this, a number of guidelines, consensus statements and recommendations regarding the management of lymphoma(s) were published at the start of the pandemic[36-43]. They invariably recommended a common-sense approach. Patients with aggressive lymphoma were to be treated as usual, while minimizing time in the hospital by use of measures including the wider use of granulocyte colony stimulating factor prophylaxis and subcutaneous administration of rituximab. In contrast, the advice for patients with more indolent lymphomas was to continue expectant management where possible and to use oral regimens where reasonable. In all cases virtual consultations were to be

encouraged, particularly for patients in complete remission or for those in which no immediate change in therapy was expected. However, there was a clear concern that patients with lymphoid malignancies were going to be at particular risk from COVID-19 due to the combined immunosuppression from their underlying disease and its treatment.

Interestingly, multiple studies have consistently reported little or no negative impact of therapy on outcomes from COVID-19. The large meta-analysis of over 3000 patients with hematological cancers showed no association of poorer outcome with concurrent treatment, as have many smaller studies[17,22]. Similarly, in the two largest lymphoma-specific COVID-19 studies, there was no association of active treatment with poor outcome[29,30]. In particular there was no excess mortality identified with anti-CD20 treatment despite the anticipated risk of depleting the B-cell compartment and inhibiting humoral immunity. While, there have been several reports of prolonged viral shedding and/or pneumonia symptoms, and failure of SARS-CoV-2 antibody responses in patients treated with rituximab, this has not translated into a significant impact on survival in the larger studies[44-46]. It is possible that modulation of the "hyperinflammatory" phase of COVID-19 is playing a role; it is also possible that the relative sparing of T-cell responses may be enough to control the virus. As a consequence, most expert bodies are recommending continuing treat lymphoid malignancies as usual whilst highlighting the importance of a risk-benefit analysis in each individual patient scenario. While there does not appear to be any additional risk from treatment *per se*, COVID-19 does pose a significant risk to lymphoma patients in itself, particularly those who are older with multiple co-morbidities. Therefore, infection with SARS-CoV-2 needs to be avoided in lymphoma patients who should generally be regarded as clinically vulnerable and advised to "shield". Visits to hospital (and hence potential exposure to the virus) should be reduced by choosing oral regimens over infusional ones where possible (*e.g.*, ibrutinib or acalabrutinib for the treatment for CLL) and avoiding treatments with marginal benefit (*e.g.*, maintenance rituximab for follicular lymphoma), particularly when COVID-19 infection rates in the general population are high.

There has been particular focus regarding the potential of ibrutinib as a potential immuno-modulator of COVID-19. Ibrutinib is used for the treatment of several B-cell disorders, including CLL, mantle cell lymphoma and Waldenstrom macroglobulinemia (WM)[47]. In addition to its inhibition of B-cell receptor signaling by Burton's tyrosine kinase (BTK) it is also known to inhibit interleukin-2 inducible T-cell kinase (ITK) modulating T-cell responses[48]. There were early reports of ibrutinib potentially having a beneficial effect in SARS-CoV-2 infection, protecting against pulmonary injury, both in the context of treatment for CLL and WM[49,50]. The effect has been hypothesized to be due not only to "off-target" inhibition of ITK, but also of inhibition of Src family kinases and attenuation of M1 macrophage polarization with the net effect of reducing viral entry and inflammatory cytokine responses in the lungs[51,52]. Whether or not the anti-platelet effect of ibrutinib could also help combat the pro-thrombotic events associated with severe COVID-19 has not been explored. Interestingly, a small clinical study has suggested that BTK inhibition could be the most important component of ibrutinib's immunomodulatory activity. Roschewski *et al*[53] assessed the efficacy of 19 patients without hematological malignancies who were hospitalized with severe COVID-19 (11 on supplemental oxygen and 8 on mechanical ventilation), 18 of whom had increasing oxygen requirements at baseline. Acalabrutinib is a more selective inhibitor of BTK and should not have any effect on ITK and Src kinases. Analysis revealed a rapid normalization of inflammatory markers such as C-reactive protein and interleukin-6 with a temporal correlation with improved oxygenation. These results suggested that targeting excessive host inflammation with a BTK inhibitor is a therapeutic strategy in severe COVID-19 and has led to an ongoing international prospective randomized controlled clinical trial. A protective effect of BTK inhibition was also observed in the European study of outcomes of CLL patients with SAR-CoV-2 infection, with lower rates of hospitalization rate for severe COVID-19 for patients on ibrutinib *vs* those on other regimens or off treatment[15]. However, an effect was not seen in the Mato *et al*[12] report, although in many cases therapy was withheld once COVID-19 was diagnosed. Again, further work is required to investigate this, but it would seem reasonable to continue BTK inhibitors in patients who are diagnosed with COVID-19 on the basis of the available evidence. Certainly, discontinuation of effective anti-lymphoma therapy has its own risks, particularly in patients with more aggressive lymphoma subtypes, as exemplified by a report of patient who developed rapid progression of their mantle cell lymphoma after ibrutinib was discontinued for intercurrent COVID-19[54].

Further questions remain around the use of other immunomodulatory drugs for lymphoid malignancies in the context of COVID-19. Immune checkpoint blockade with drugs targeting programmed cell death 1 and other immuno-inhibitory molecules is widely used in the solid cancer field where they "release the brakes" of immune tolerance mechanisms leading to effective anti-tumor responses[55]. These agents are less commonly used in lymphoma where the main indications are in relapsed Hodgkin lymphoma and Richter syndrome. Again, the potential impact of immune checkpoint blockade in patients with COVID-19 could be hypothesized to be double-edged, with these agents potentially enhancing immunological control of the viral infection, yet also contributing to inflammation and aggravating the clinical course of COVID-19. Reports of these drugs in lymphoma are currently limited to a single case report. O'Kelly *et al*[56] report a case of a 22 year-old female with multiply relapsed Hodgkin lymphoma having pembrolizumab who developed severe COVID-19 requiring high levels of oxygen supplementation but not intubation, who subsequently recovered. A recently published study of 35 patients receiving immune checkpoint blockade in solid cancers concluded that COVID-19 related mortality in this population did not appear to be higher than previously published mortality rates for patients with cancer suggesting that this type of treatment does not increase the risk[57]. Another class of anti-lymphoma drugs that could be hypothesized to have an impact on the course of COVID-19 are the immunomodulatory imide drugs such as thalidomide and lenalidomide. While being used most commonly in the treatment of multiple myeloma, lenalidomide is well known to have activity in lymphomas including follicular lymphoma, mantle cell lymphoma and CLL[58,59]. At the time of writing the reports of the impact of these drugs on COVID-19 outcomes in myeloma patients remain equivocal; there are no reports of the outcome of COVID-19 with intercurrent use of these drugs in lymphoma. The potential mechanisms by which treatments for lymphoma may modulate COVID-19 infection is summarized in Figure 1.

A discussion of the general principles of managing severe COVID-19 in lymphoid malignancies is beyond the scope of this review. However, one aspect that might be expected to be specifically relevant to these cancers is the use of convalescent plasma to treat COVID-19, given the hypogammaglobulinemia that frequently observed, particularly in CLL. As intravenous immunoglobulin replacement is indicated to prevent infections in these patients, it is reasonable to hypothesize that plasma containing anti-SARS-CoV-2 antibodies might be of particular benefit in these patient groups. Several studies have now looked at the efficacy of convalescent plasma in the general population. Initial randomized trials of convalescent plasma in patients with COVID-19 focused on hospitalized patients who were already moderately to severely ill, with these trials providing little evidence of clinical efficacy[60,61]. Subsequent observational studies have been more positive but generally the clinical benefits have been modest[62]. However, a recent randomized study has suggested that this "passive immunotherapy" can be effective if the right plasma is used for the right patients, with early administration of high-titer convalescent plasma against SARS-CoV-2 to mildly affected older adults reducing the progression of COVID-19[63]. While there have been no randomised studies investigating the use of convalescent plasma in patients with lymphoid malignancies, there have been several case reports and observational case series reporting efficacy in this patient group[64-70]. As a consequence, it seems reasonable to use convalescent plasma for high risk individuals in this patient group as long as the plasma contains high titers of SARS-CoV-2 antibodies and is given early enough in the patient's course of infection.

IMPACT OF COVID-19 ON HEMOPOIETIC STEM CELL TRANSPLANTATION OF LYMPHOMA

High-dose chemotherapy with autologous hemopoietic stem cell transplantation (HSCT) represents a standard of care for many lymphoid malignancies, with allogeneic HSCT being potentially curative for other particular indications. Both types of transplantation are scenarios where COVID-19 infection could be expected to lead to particularly severe consequences, given the state of immune suppression that they induce. As a consequence, transplant organizations such as the European Society for Blood and Marrow Transplantation (EBMT) have been regularly issuing and updating recommendations regarding all aspects of transplantation during the pandemic[71]. The EBMT has been collecting data regarding the impact of COVID-19 on HSCT recipients and also those undergoing treatment with chimeric antigen receptor (CAR)

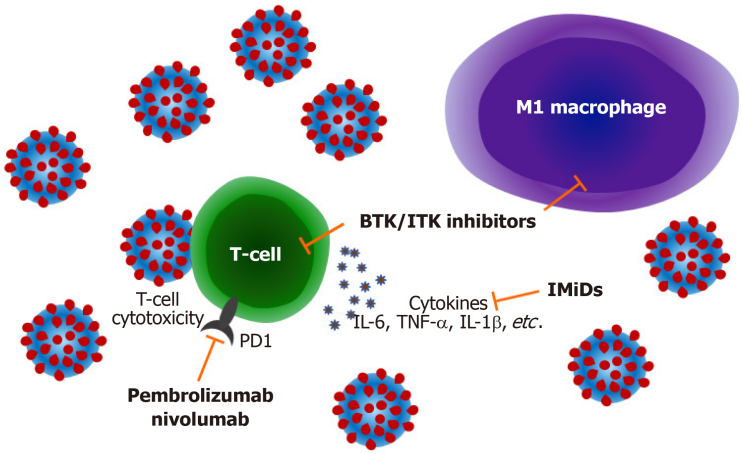

Figure 1 Mechanisms by which lymphoma treatments may modulate coronavirus disease 2019 infection. Inhibition of Burton's tyrosine kinase and interleukin-2 inducible T-cell kinase modulates T-cell immune responses decreasing production of pro-inflammatory cytokines such as interleukin-6, tumour necrosis factor α and interleukin-1b and also attenuating M1 macrophage polarization reducing pulmonary inflammation. Immune checkpoint blockade with drugs targeting programmed cell death 1 may improve antiviral cytotoxic T-cell responses. Immunomodulatory imide drugs can also block cytokine responses and improve T-cell function. BTK: Burton's tyrosine kinase; ITK: Interleukin-2 inducible T-cell kinase; PD1: Programmed cell death 1; IMiDs: Immunomodulatory imide drugs; IL: Interleukin; TNF-α: Tumour necrosis factor α.

T cells. While the 6-wk mortality in this patient group in the 1st wave was approximately 25%, preliminary data from the 2nd wave (August to December 2020) suggests a mortality rate slightly below 20%. This figure is not too dissimilar to that published by the group at the Memorial Sloan Kettering Cancer Center who observed that 22% of patients who had received cellular therapy (Allogeneic, 35; Auto, 37; CAR T, 5) had died after 30 d[72]. Notably the largest study published to-date did not observe any differences in 30-d overall survival when comparing recipients of allogeneic *vs* autologous HSCT[73]. Despite the theoretical risks associated with the procedure itself, the very nature of determining an individual's eligibility for transplant typically excludes those at higher risk from COVID-19, which probably explains why these figures are lower than the fatality rates seen for patients with hematological malignancies outside the transplant setting. Many of the recommendations focus on avoiding SARS-CoV-2 infection by limiting risk of exposure to infected individuals as much as possible and strictly adherence to prevention practices such as hand hygiene and social distancing—something that applies to the donor as well as the recipient in allogeneic transplants[74]. The challenging question is what to do in patients that develop COVID-19 during preparation for transplantation? This includes those that acquire COVID-19 immediately before transplantation and those that develop and recover but have a persistently positive polymerase chain reaction test. Generally, the decision to proceed has to be assessed on a case-by-case basis weighing in the risks from COVID-19 infection *vs* the risks from delaying the transplant. The grade of lymphoid malignant (indolent *vs* aggressive) and availability of alternative salvage therapy will clearly play into these decisions. In addition to ongoing data collection by the bone marrow transplant registries there are now several published case reports and case series of patients successfully completing a bone marrow transplant despite intercurrent SARS-CoV-2 infection, including one report where all 11 patients survived without oxygen supplementation or mechanical ventilation[72,73,75-78]. Despite this, risks for lymphoma patients remain, with one study reporting a higher risk of mortality in autologous HSCT recipients when the indication was for lymphoma compared to myeloma—likely reflecting the increased intensity of the multi-agent high-dose chemotherapy used in lymphoma autograft conditioning[73]. Other potential factors identified as being predictive of poorer outcomes in HSCT include older age, being on steroids at the time of diagnosis of COVID-19, and COVID-19 infection within 1 year of HSCT[16].

IMPACT OF LYMPHOMA ON VACCINATION FOR COVID-19

The enormous societal and economic impact of the pandemic made it a global emergency to develop effective vaccines. In a testament to human ingenuity the first SAR-CoV-2 vaccine trails were being reported less than a year after the virus was

initially identified[79-81]. A number of vaccines are in production with efficacy against laboratory-confirmed infection typically greater than 90%. Not surprisingly, the trials have excluded patients on treatment with immunosuppressive therapy or those diagnosis with an immunocompromising condition, which includes all patients with lymphoid malignancies. Therefore, at the time of writing there is no data on the efficacy of any of the leading SARS-CoV-2 vaccines in patients with lymphoid malignancies. As discussed above patients with these cancers could be expected to fail to mount an immune response to these vaccines. This is due both to the immune defects associated with the diseases themselves and also due to the impact of treatments. While little is known about the efficacy of COVID-19 vaccines in lymphoma patients, plenty of studies have demonstrated reduced rates of sero-conversion in patients vaccinated for other viruses in the past. Furthermore, one-third of CLL patients who had COVID-19 failed to mount a persistent antibody response in one study[69]. Therefore, it will be vital to design studies to assess their efficacy in patients with lymphoid malignancies, as even if current vaccines achieve the ideal of "herd immunity", the presence of SARS-CoV-2 mutant strains will likely mean that lymphoma patients still require direct protection[82]. A further consideration is perhaps the opposite problem. As vaccines are widely rolled-out some patients with lymphoid malignancies will receive one or more doses during therapy. We have seen several cases at our centre when vaccination results in an increase in glycolytic lymphadenopathy as part of the normal immune response, something that can mimic lymphoma progression on fludeoxyglucose positron emission tomography/computed tomography[83].

CONCLUSION

The COVID-19 pandemic has been a challenge for all sections of society across the world. Despite this, a great deal has been learnt about this virus in a very short space of time, including its impact in patients with hematological malignancies. Multiple studies have consistently demonstrated that approximately one-third of patients with blood cancers who acquire COVID-19 and have it severely enough to require hospital assessment will die, representing a slightly greater than 2-fold increased risk compared to the general population. Perhaps surprisingly, several studies have shown little or no negative impact of concurrent or recent anti-cancer therapy on outcomes from COVID-19, with reports of agents such as the BTK inhibitors actually having a protective effect. This is important as it means that treatment should be initiated and continued as required, rather than being delayed due to concerns regarding the risks from COVID-19. Instead, the focus needs to be stopping lymphoma patients from acquiring SARS-CoV-2 in the first place, by advising them to shield and taking steps to reduce hospital visits. However, a great deal still remains unknown about the impact of this infection in patients with lymphoid malignancies. Particular questions remain around the outcomes of COVID-19 in rarer lymphomas, and about the interaction between lymphoma-associated and treatment-induced immunosuppression and vaccine responses. While it can be anticipated that these gaps in our knowledge will start to become filled over the coming months, the presence of novel SARS-CoV-2 mutants will almost certainly mean that many years of work lie ahead.

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EVIDENCE-BASED MEDICINE

Association between population vitamin D status and SARS-CoV-2 related serious-critical illness and deaths: An ecological integrative approach

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Abstract

BACKGROUND

Vitamin D population status may have possible unappreciated consequences to the coronavirus disease 2019 (COVID-19) pandemic. A significant association between vitamin D sufficiency and reduction in clinical severity and inpatient mortality from COVID-19 disease has recently been shown, while a recent study has claimed lower COVID-19 cases in European countries with a better vitamin D status. Low serum 25-hydroxyvitamin-D [25(OH)D] was identified as an independent risk factor for COVID-19 infection and hospitalization, and administration of 0.532 mg (21280 IU) of calcifediol or 25(OH)D, followed by 0.266 mg on days 3 and 7 and then weekly until discharge or intensive care unit admission significantly reduced the need for intensive care unit treatment.

AIM

To elucidate the role of vitamin D European population status in the COVID-19 pandemic, data from the Worldometer were analyzed.

METHODS

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Linear regression explored the correlation between published representative-standardized population vitamin D concentrations and the number of total cases/million (M), recovered/M, deaths/M and serious-critically ill/M from COVID-19 for 26 European countries populated > 4 M (Worldometer). Life expectancy was analyzed with semi-parametric regression. Weighted analysis of variance/analysis of covariance evaluated serious-critical/M and deaths/M by the vitamin D population status: Deficient < 50, insufficient: 50-62.5, mildly insufficient > 62.5-75 and sufficient > 75 nmol/L, while controlling for life expectancy for deaths/M. Statistical analyses were performed in XLSTAT LIFE SCIENCE and R (SemiPar Library).

RESULTS

Linear regression found no correlation between population vitamin D concentrations and the total cases-recovered/M, but negative correlations predicting a reduction of 47%-64%-80% in serious-critical illnesses/M and of 61%-82%-102.4% in deaths/M further enhanced when adapting for life expectancy by 133-177-221% if 25(OH)D concentrations reach 100-125-150 nmol/L, sustained on August 15, 2020, indicating a truthful association. Weighted analysis of variance was performed to evaluate serious-critical/M ($r^2 = 0.22$) by the vitamin D population status and analysis of covariance the deaths/M ($r^2 = 0.629$) controlling for life expectancy ($r^2 = 0.47$). Serious-critical showed a decreasing trend ($P < 0.001$) from population status deficient ($P < 0.001$) to insufficient by 9.2% ($P < 0.001$), to mildly insufficient by 47.6% ($P < 0.044$) and to sufficient by 100% (reference, $P < 0.001$). For deaths/M the respective decreasing trend ($P < 0.001$) was 62.9% from deficient ($P < 0.001$) to insufficient ($P < 0.001$), 65.15% to mildly insufficient ($P < 0.001$) and 78.8% to sufficient ($P = 0.041$).

CONCLUSION

Achieving serum 25(OH)D 100-150 nmol/L (40-60 ng/mL) (upper tolerable daily doses followed by maintenance proposed doses not requiring medical supervision, Endocrine Society) may protect from serious-critical illness/death from COVID-19 disease.

Key Words: COVID-19; SARS-CoV-2; Vitamin D status; Vitamin D concentrations; 25-hydroxyvitamin-D; Immunity

Core Tip: To elucidate the role of vitamin D in the coronavirus disease 2019 (COVID-19) pandemic, we examined associations between published representative and standardized European population vitamin D data and the Worldometer COVID-19 data. Linear regression found no correlation between population vitamin D concentrations and the total cases-recovered/million (M), but negative correlations predicting a reduction of 47%-64%-80% in serious-critical illnesses/M and of 61%-82%-102.4% in deaths/M further enhanced when adapting for life expectancy by 133-177-221% if 25-hydroxyvitamin-D concentrations reach 100-125-150 nmol/L. Weighted analysis of variance/analysis of covariance showed a decreasing trend ($P < 0.001$) evaluating serious-critical/M ($r^2 = 0.22$) and the deaths/M ($r^2 = 0.629$) after controlling for life expectancy ($r^2 = 0.47$), by vitamin D population status, respectively.

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INTRODUCTION

Vitamin D deficiency and insufficiency is a global health issue affecting probably many more than 1 billion children and adults worldwide, with institutionalized elderly being at higher risk of exhibiting lower 25-hydroxyvitamin-D [25(OH)D] blood concentrations. According to a systematic review of vitamin D status in populations worldwide, 37.3% of the studies reported 25(OH)D mean concentrations < 50 nmol/L in newborns and institutionalized elderly, who are at higher risk of exhibiting lower 25(OH)D concentrations[1]. Public health policy development is needed to reduce risk for potential health consequences of an inadequate vitamin D status[1], with consequences that should not be underestimated, especially now with this unprecedented pandemic of coronavirus disease 2019 (COVID-19)[2]. The initial universal lockdown for a period of 2-3 mo and the consequent repeated lockdowns along with the social distancing measures would further reduce the incidental solar vitamin D3 production, worsening the population's vitamin D status[3]. Strong evidence supports the role of vitamin D particularly in preventing rickets and osteomalacia[4]. While circulating 25(OH)D concentrations below 30 nmol/L (12 ng/mL) are associated with an increased risk of rickets/osteomalacia, 25(OH)D concentrations between 50-125 nmol/L (20-50 ng/mL) appear to be safe and sufficient to promote skeletal health in the general population[5]. A serum 25(OH)D concentration of at least ≥ 50 nmol/L at the end of winter (10-20 nmol/L higher at the end of summer, to allow for seasonal decrease) is required for optimal musculoskeletal health[6]. Supplements of vitamin D in low doses together with calcium, alone or in combination with antiresorptive drugs may prevent hip or any type of fracture and have been evaluated in osteoporotic and osteopenic patients for primary as well as secondary prevention[7-9]. However, the role of vitamin D in innate and adaptive immunity remains rather underappreciated, with possible consequences and public health implications, leading to an increased risk for infectious diseases, autoimmune disorders and cancers[10]. Even if a recent randomized control trial (RCT) did not show lower incidence of invasive cancer in men ≥ 50 years or women ≥ 55 receiving 2000 IU of vitamin D3 daily up to 5 years[11], the study did report a statistically significant 25% reduced risk for cancer mortality. The study, however, had several limitations. Only 13% of the participants were vitamin D deficient [25(OH)D < 50 nmol/L], and 42%-45% of the participants were receiving a vitamin D supplement and multivitamins at inclusion. The participants, including the placebo group, were permitted to take up to 800 IU of vitamin D daily. This is the likely explanation why the mean baseline blood concentration of 25(OH)D was 74.5 nmol/L for the participants in this study[11]. The optimal 25(OH)D concentration is at least 75 nmol/L (30 ng/mL), which is what the mean baseline level was for the participants in the VITAL study. Secondary analyses from the VITAL study should be also considered as they indicate that the vitamin D dose was too low, since significant benefits were found for cancer incidence for those with body mass index (BMI) < 25 kg/m^2 and almost as significant for blacks. In fact, the authors speculated that the possible trial regimen–associated effects on cancer incidence among normal-weight participants and suggestive effects among black participants, which contrast with the null cardiovascular findings in these groups, may be explained by different vitamin D requirements for these outcomes. The Endocrine Society, which made its recommendations in 2011 for the treatment and prevention of vitamin D deficiency, concluded that to guarantee bone health, a blood level of 25(OH)D of at least 75 nmol/L (30 ng/mL) is required (https://www.endocrine.org/clinical-practice-guidelines/vitamin-d-deficiency)[12]. Beyond musculoskeletal health however, it has been found that vitamin D supplementation significantly reduced the risk of cancer death by 15% in a systematic review and meta-analysis of 52 trials with a total of 75454 participants[13], and it has been suggested that better health outcomes may occur in the range of 100-150 nmol/L[10]. The largest meta-analysis ever conducted of all studies published between January 1, 1966 and January 15, 2013 dealing with all-cause mortality related to serum 25(OH)D showed that 25(OH)D < 75 nmol/L was associated with higher all-cause mortality, its reduction being maintained with 25(OH)D ≥ 175 nmol/L (70 ng/mL), without a U-shaped curve as previously reported[10]. Achieving such concentrations with supplements and sensible sun exposure for a normal weight adult requires 2000–5000 IU daily intake of vitamin D2/D3, practically all year long except maybe during sunny vacations[14]. With vitamin D adequacy relying mainly (80%-90%) on sun exposure rather than on dietary sources (10%-20%), if not on supplementation, these doses should be adapted accordingly during lockdowns. It should also be recognized that sensible sun exposure has many additional health benefits not only in the immune system but also in

improving the feeling of well-being[15]. At this time, neither the World Health Organization nor any other public health authority has issued any official advice or recommendation on vitamin D, or any other nutrients, to the best of our knowledge.

A quadratic relationship was found between vitamin D deficiency in countries affected by COVID-19 and the latitudes, implying a possible relation[16]. When mortality/ million (M) is plotted against latitude, all countries below 35 degrees North, above which people do not receive sufficient sunlight to retain adequate 25(OH)D concentrations during winter, have relatively lower mortality, implying a role for vitamin D status in outcomes from COVID-19[17]. Vitamin D is strongly affected by ozone variability, since ozone filters ultraviolet B, an important factor for vitamin D synthesis. A statistically significant link between ozone concentration and incidence of COVID-2019 disease in 34 countries was established[18]. Going back to the 1918-1919 influenza pandemic, substantial correlations were found for associations of July ultraviolet B dose in the United States with case fatality rates and rates of pneumonia[19]. A significant association between vitamin D sufficiency and reduction in clinical severity and inpatient mortality was very recently shown[20]. Thus, to elucidate further the possible role of vitamin D population status in the COVID-19 pandemic, we examined the associations between published representative and standardized population vitamin D data on European population vitamin D status and the Worldometer COVID-19 data.

MATERIALS AND METHODS

Accessing data on European countries at the Worldometer, on June 19, 2020, we analyzed the 28 countries populated > 4 M (Table 1). For months, Swedish public health authorities have defended their controversial decision not to lock down the country in response to the global COVID-19 pandemic, with the country experiencing dramatic casualties. Thus, Sweden was excluded from analysis. The remaining 27 European countries adopted a defensive strategy during the current pandemic, even with delays and hesitations, as in the United Kingdom. Moldova was also excluded as no published vitamin D status data were found. For the remaining 26 countries, we used linear regression to explore the correlation between reported representative and standardized population vitamin D concentrations[21-28] and the number of total cases/M and recovered/M until June 19, 2020 as well as the deaths/M and the serious-critically ill/M from COVID-19 on that date (Table 1). Since mortality of COVID-19 disease has been shown to increase rapidly in respect to age, life expectancy (LE), an age-related index, was analyzed using a semi-parametric regression approach using Worldometer data. Weighted (https://doi.org/10.13094/SMIF-2015-00001) analysis of variance (ANOVA)/analysis of covariance (ANCOVA) was performed to evaluate serious-critical/M and deaths/M by the vitamin D population status - categorized as deficient (D) < 50, insufficient (IN) 50-62.5, mildly insufficient (MIN) > 62.5-75 and sufficient (S) > 75 nmol/L – while controlling for LE for deaths/M. To test whether these correlations withstand at another completely different momentum of this pandemic, which would be an indication of a truthful association, although still not a proof of causality, we also checked the above correlations and the differences between consecutive points of the same variables on August 15, 2020. All statistical analyses were performed in XLSTAT LIFE SCIENCE version April 1, 2020 (copyright Addinsoft 1995-2020) and R (R Core Team 2017), with the use of the SemiPar library.

RESULTS

From the 26 European countries included in the analysis, populated 714.661 M in total, nine (54.17%, 387.15 M) had a vitamin D deficient status, eight an insufficient status (33.58%, 240.022 M), eight a mild insufficiency status (11.48%, 82.023 M) and only one country, Slovakia, a sufficient status (0.76%, 5.459 M). There was no correlation between the total cases/M nor the recovered/M and the European population vitamin D concentrations. Negative correlations were recognized regarding the total deaths/M (Figure 1A), predicting a reduction of deaths/M by 20% if the 25(OH)D concentration reaches 50 nmol/L (related to the number calculated at 25), by 40% at 75, by 61% at 100, by 82% at 125 and by 102.4% at 150 nmol/L and the serious-critical/M (Figure 1B), predicting a reduction of serious-critically ill/M by 16% if 25(OH)D concentration reaches 50 nmol/L (related to the number calculated at 25), by 31% at 75, by 47% at 100, by 64% at 125 and by 80% at 150 nmol/L.

Table 1 European coronavirus disease 2019 data from the Worldometer on June 19, 2020, compared to life expectancy and to available representative and standardized data on the European population vitamin D status[21-28]

	Country	Total cases/M	Total recovered	Serious critical	Deaths/M	Life expectancy in yr	Population 25(OH)D in nmol/L	Population, M
1	Russia	3899	324406	2300	54	72.99	39.7	145.93
2	Germany	2273	174400	396	107	81.88	50.1	83.77
3	United Kingdom	4447	N/A	379	626	81.77	47.4	67.87
4	France	2431	73887	752	454	83.13	60.0	65.26
5	Italy	3939	180544	168	571	84.01	45.0	60.46
6	Spain	6253	N/A	617	580	83.99	59.9	46.75
7	Ukraine	800	16033	343	23	72.50	29.0	43.74
8	Poland	827	15698	87	35	79.27	32.0	37.84
9	Romania	1216	16555	184	77	76.50	65.0	19.24
10	Netherlands	2885	N/A	57	355	82.78	64.7	17.13
11	Belgium	5219	16751	55	837	82.17	49.3	11.58
12	Czechia	968	7472	9	31	79.85	62.5	10.70
13	Greece	311	1374	10	18	82.80	54.3	10.42
14	Portugal	3772	24477	67	150	82.65	55.4	9.66
15	Sweden	5550	N/A	272	500	83.33	68.7	9.44
16	Hungary	422	2581	15	59	77.31	60.6	83.33
17	Belarus	6067	35275	92	36	75.20	72.0	9.00
18	Austria	1918	16141	7	76	82.05	51.7	8.73
19	Serbia	1454	11511	18	30	76.47	65.7	8.65
20	Switzerland	3,608	28900	17	226	84.25	46.0	6.94
21	Bulgaria	529	1941	13	27	75.49	38.7	5.79
22	Denmark	2139	11282	6	104	81.40	65.0	5.54
23	Finland	1287	6200	2	59	82.48	67.7	5.45
24	Slovakia	289	1447	0	5	78.00	81.5	5.41
25	Norway	1,609	8138	5	45	82.94	71.0	4.93
26	Ireland	5137	22698	28	347	82.81	56.4	4.10
27	Croatia	555	2142	0	26	79.02	46.9	4.03
28	Moldova	3249	7525	455	111	72.30	N/A	10.09

25(OH)D: 25-hydroxyvitamin-D; M: Million.

Population vitamin D concentrations *vs* life expectancy exhibits a non-linear relationship (Figure 2): Higher life expectancy until approximately 77 years of age is characterized by better vitamin D concentrations, while practically reaching a plateau at 82 years, and then by a decline as expected in the elderly. There is a non-linear relationship between life expectancy and deaths/M with a dramatic increase in deaths/M after approximately 80 years (Figure 3). LE (*i.e.* age) seems to interfere with the effect of a better vitamin D concentration to the total number of deaths/M, rendering the vitamin D benefit even more important than the unadjusted one: A reduction in total deaths/M by 44% if 25(OH)D concentration reaches 50 nmol/L (related to the number calculated at 25), by 88% at 75, by 133% at 100, by 177% at 125 and by 221% at 150 nmol/L. The analytical form for the model on the deaths/M accounting for a potential non-linear effect of LE is year = -2675-4.111*vitamin D + f(LE), where f(.) is a non-linear smooth function of life expectancy. The *P* value for the

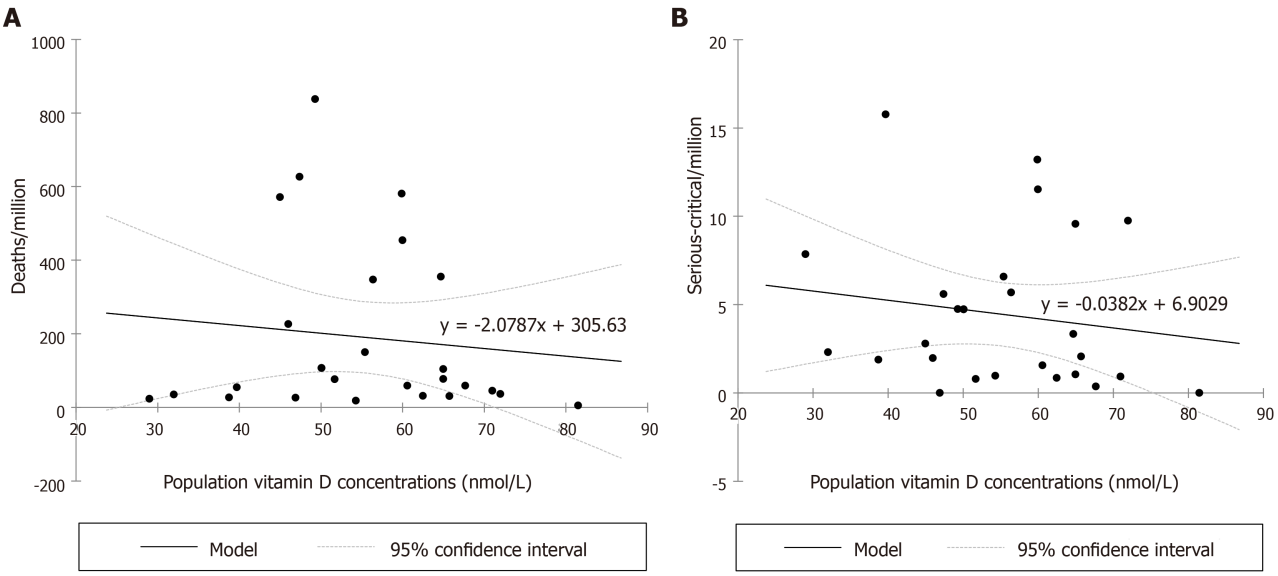

Figure 1 Linear regression on June 19, 2020 related to available representative and standardized data on the European population vitamin D concentrations (x axis, nmol/L). A: Of the total deaths/million (M); B: Of the serious-critical cases/M.

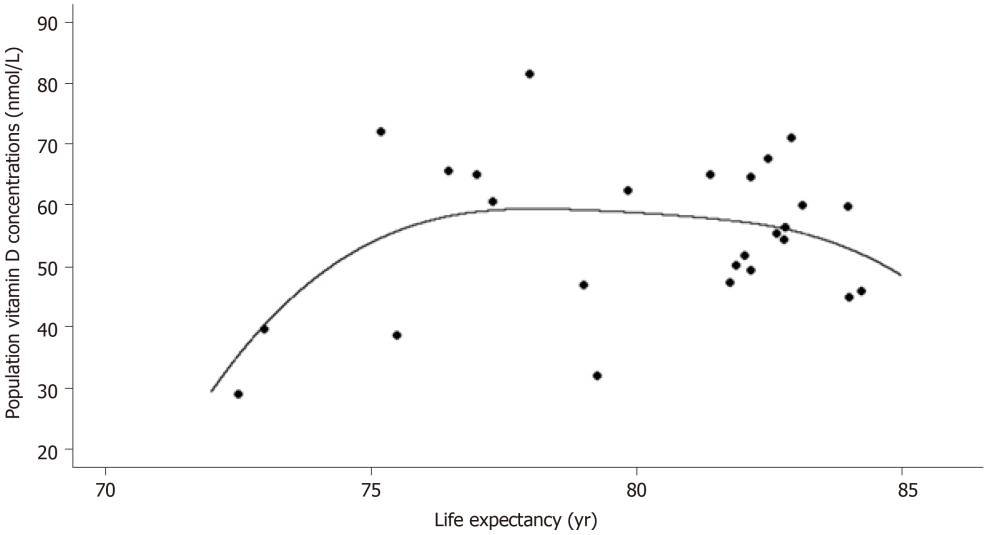

Figure 2 Population vitamin D concentrations *vs* life expectancy exhibits a non-linear relationship.

term f(LE) was estimated *via* likelihood ratio test to be $P = 0.042$, indicating a statistically significant effect of life expectancy on deaths/M after adjusting for vitamin D concentration.

Weighted (https://doi.org/10.13094/SMIF-2015-00001) ANOVA was performed to evaluate serious-critical/M and ANCOVA for deaths/M by the population vitamin D status while controlling for LE. Given the r^2, about 22% of the variability of the dependent variable serious-critical/M could be explained by the population vitamin D status. A decreasing trend from population status D [β = 8.684, standard error (SE) = 2.196, 95% confidence interval (CI): 4.372/12.996, $P < 0.001$], IN (β = 7.883, SE = 2.205, 95%CI: 3.553/12.213, $P < 0.001$), MIN (β = 4.548, SE = 2.252, 95%CI: 0.126/8.169, $P = 0.044$) to S (LE mean 0.0, SE 2.181, 95%CI: -4.282/4.282, $P < 0.001$) was found with an average reduction of serious-critical/M of 9.2% from vitamin D status deficient to insufficient, of 47.6% from deficient to mildly insufficient and 100% from deficient to sufficient (reference, Figure 4). Regarding deaths/M (Figure 5), given the r^2, about 63% of the variability of the dependent variable deaths/M could be explained by the two variables, LE alone accounting for 47%. A decreasing trend from population status deficient (β = 150.375, SE = 8.859, 95%CI: 132.982/167.768, $P < 0.001$), insufficient (β = -72.514, SE = 10.336, 95%CI: -150.170/-55.866, $P < 0.001$), mildly insufficient (β =

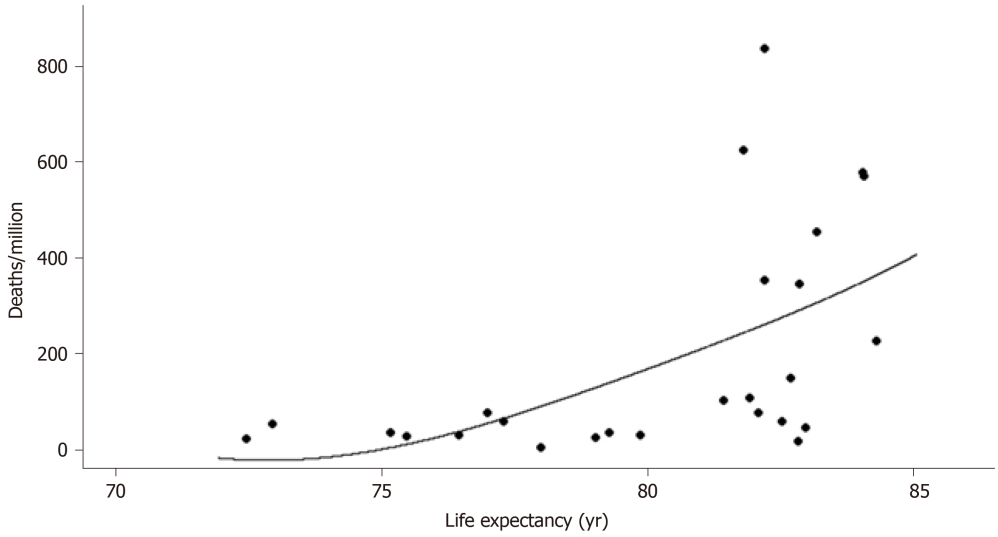

Figure 3 Non-linear relationship between life expectancy and deaths/million.

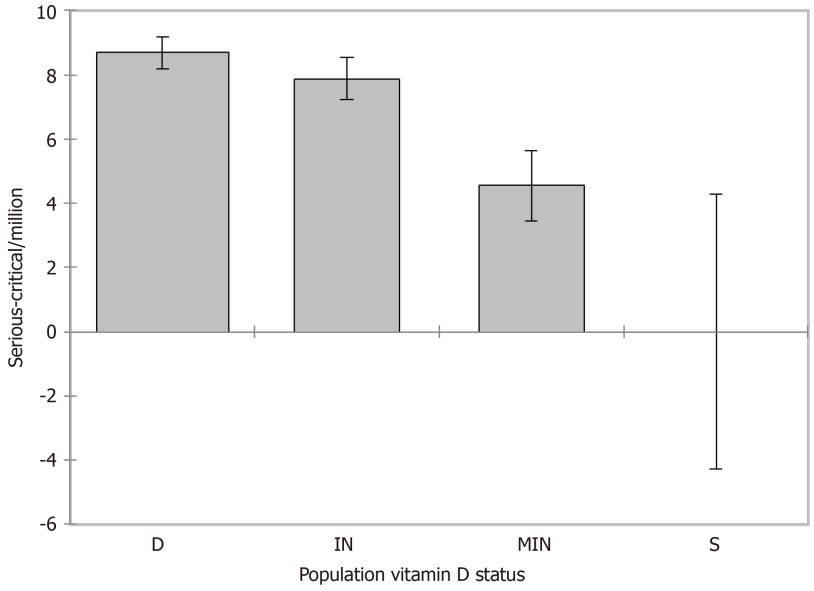

Figure 4 Least square means of serious-critical/million for factor population vitamin D status. D: Deficiency; IN: Insufficiency; MIN: Mild insufficiency; S: Sufficiency.

-80.518, SE = 12.556, 95%CI: -105.170/-55.866, $P < 0.001$) to sufficient (β = -129.122, SE = 62.915, 95%CI: -252.644/-5.599, $P = 0.041$) was found with an average reduction of deaths/M of 62.9% from vitamin D status deficient to insufficient, of 65.15% from deficient to mildly insufficient and 78.8% from deficient to sufficient.

On August 15, 2020, the above correlations were sustained and the differences between consecutive points for the two variables serious-critical/M and deaths/M in the two time points were correlated, not proving causality but suggesting a truthful association.

DISCUSSION

We explored any possible correlation between the population vitamin D status - influenced by various factors - and COVID-19 disease, in particular total cases, serious-critical illness and deaths. In contrast to a recently published study[29], we found no association between the vitamin D status of the European populations and the total confirmed cases/M of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)

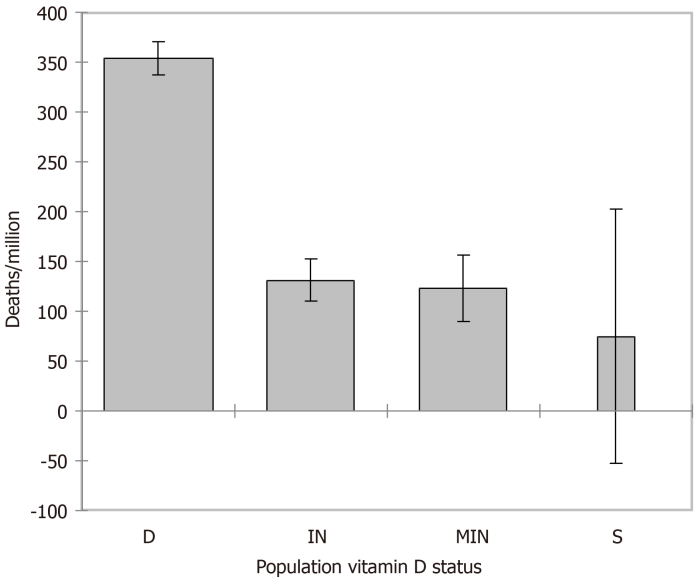

Figure 5 Least square means of deaths/million for factor population vitamin D status. D: Deficiency; IN: Insufficiency; MIN: Mild insufficiency; S: Sufficiency.

infections when we analyzed data from the Worldometer on June 19, 2020 on 26 European countries populated > 4 M. However, the negative correlations that we found between population vitamin D status and serious-critical/M and deaths/M show a clear tendency, even if they do not prove causality, namely after adjusting for LE, underlining the importance of an optimal vitamin D status especially in the elderly[30]. On August 15, 2020, at a completely different time point of this pandemic, before the second wave even had started, the above associations were sustained, suggesting a truthful correlation. Since the risk of COVID-19 disease increases rapidly with respect to age, an age-related index, such as LE, was found, as expected, to be a more important predictor of death rates. Thus, according to our results, a higher 25(OH)D concentration may protect from serious-critical illness and death from COVID-19 disease even more in the elderly but does not seem to prevent SARS-CoV-2 from spreading, in contrast to a recent study[29], which however reported also a negative correlation between the mean population vitamin D concentrations of 20 European countries and deaths/M from COVID-19 on April 8, 2020. Our findings also coincide with a recent study from Maghbooli *et al*[20] showing that vitamin D sufficiency [a serum 25(OH)D > 75 nmol/L (30 ng/mL)] reduced risk for adverse clinical outcomes in patients with COVID-19 infection: 6.3% of the patients who had a blood 25(OH)D concentration of at least 100 nmol/L (40 ng/mL) succumbed to the infection compared to 9.7% and 20% who died and had a circulating blood level above and below 75 nmol/L (30 ng/mL), respectively[20,31], suggesting that a blood level of at least 100 nmol/L (40 ng/mL) may be optimal for obtaining vitamin D's immunomodulatory benefit.

Various parameters played a significant role in the spread of the current pandemic. Among them, air travel and direct connections with China and particularly Wuhan, where the epidemic started. Then, health policymaking with mass quarantine was instituted in most countries, influencing the course of the disease, but with no central coordination of the measures taken during the first wave of the pandemic, not even in the core of the European Union itself. Timing of the lockdowns, at least in the first wave, seemed to have been the main factor affecting the number of the cumulative deaths – although this has been strongly debated (https://thefatemperor.com/published-papers-and-data-on-lockdown-weak-efficacy-and-lockdown-huge-harms/), along with travel and border restrictions. Recent research emphasizes the importance of face masks while self-protection measures seem to be better implemented by populations with higher educational levels. Temperature also appears to have a small but statistically significant impact on the viral transmission rate as countries with daily average temperatures below 20 °C had a faster transmission rate. Most probably, genetic predisposition must have played a fundamental role in the susceptibility in SARS-CoV-2 infection[32,33]. The recent discovery of robust genetic signals relating to key host antiviral defense mechanisms and mediators of inflammatory organ damage

in COVID-19 may lead to targeted treatment with existing drugs[33]. Most recent evidence show that angiotensin-I converting enzyme-2 (ACE2) expression and/or polymorphism could also influence both the individual susceptibility to SARS-CoV-2 infection and the outcome of the COVID-19 disease[34]. Thus, the integrity of our immune system and its ability to fight back with a coordinated way, keeping asymptomatic or within the subclinical spectrum most of the people infected and saving the lives of the severely infected, is a crucial factor. And there is significant evidence that vitamin D deficiency may compromise both innate and acquired immunity responses, leading to increased vulnerability to infections as to autoimmune responses and disorders[35].

The vitamin D status of a population is dependent on a variety of factors including supplementation and food fortification strategies, latitude of the country, season as well as on the local nutritional and sun exposure habits, especially in the non-institutionalized elderly[36]. The vitamin D status in the winter is even lower[1,37,38], with underappreciated consequences to the immune function[39,40]. Ideally, we should be able to analyze data on vitamin D status of the elderly in winter. Thus, a major limitation of our ecological approach is that we had to rely on published - but perhaps not always completely representative - data on the vitamin D status of the populations in Europe. However, data analyzed are based mainly on "Current vitamin D status in European and Middle East countries and strategies to prevent vitamin D deficiency: A position statement of the European Calcified Tissue Society" recently published in the European Journal of Endocrinology[21] – presenting not only representative nationally or regionally as possible but also standardized population vitamin D concentrations -, a systematic review of vitamin D status in southern European countries[22], and a very important study applying the protocols developed by the National Institutes of Health-led international Vitamin D Standardization Program to serum 25(OH)D data from representative childhood/teenage and adult/older (we chose data from older adults) European populations, representing a sizable geographical footprint, to better quantify the prevalence of vitamin D deficiency in Europe[28]. Keeping in mind that the population vitamin D status reflects that of the elderly, which by default will be worse, we tried to analyze the most recently validated and representative data possible, whereas from the available data for each country we chose data from older adults in winter where provided, and in any case from Caucasian descent. Ideally, we should be able to analyze data on 25(OH)D concentrations of the patients as in an interesting recent report from Switzerland, which found significantly lower circulating 25(OH)D concentrations [27.75 nmol/L (11.1 ng/mL), $P = 0.004$] in polymerase chain reaction-positive for SARS-CoV-2 patients compared with negative patients [61.5 nmol/L (24.6 ng/mL)], even after stratifying patients according to age > 70 years[41]. Another important issue would be the differences in assessment mainly of the COVID-19 deaths in the various European countries. However, the World Health Organization had already issued the "International guidelines for certification and classification (coding) of COVID-19 as cause of death, April 20, 2020" 2 mo earlier to our analysis, allowing us to assume that they must had already been adopted by the European Countries responsible public health authorities. Furthermore, Worldometer.info mainly collects data from official reports, directly from governmental communication channels. An additional important limitation is the true evaluation of the number of affected subjects in the variable countries: Since not all patients infected with COVID-19 are symptomatic, the cases/M are dependent upon the percentage of the population tested and the consistency of the frequency of testing during the disease period evaluated, not to mention that several patients or carriers have been tested several times. Furthermore, the definition of case includes a carrier as well as a patient. Unfortunately, this limitation could not be overcome with the publicly available COVID-19 data at the time of our analysis. However, we had to report the absence of any correlation between total cases/M and the population vitamin D status in the sample we analyzed, in contrast to a recently published study with the opposite results[29]. Assessment of serious-critical cases in the European countries may also have been limited at some points by the shortcoming of intensive care unit (ICU) beds as well as the introduction of different drugs and "cocktail" treatments from country to country. Albeit, on June 19, 2020, the first wave of the pandemic in Europe was kind of winding down, and not particularly effective new or repurposed medication had at least been qualified at that point as such to change significantly the clinical course of the serious-critical patients, other than the accumulated experience of the health workers fighting on the frontline.

Independent researchers increasingly call for optimization of vitamin D status for enhanced immune protection against COVID-19 at least in older adults, hospital inpatients, nursing home residents and other vulnerable groups, extending this

recommendation to the general population[42]. The elderly (> 65 years) have a higher risk for vitamin D deficiency due to decreased sun exposure and reduced ability for cutaneous synthesis[38], whereas aging exerts significant effects on all cells of the innate immune system[40], making vitamin D sufficiency even more valuable in this group. Early nutritional supplementation in non-critically ill patients hospitalized for COVID-19 has been implemented in hospital protocols providing 50000 UI/wk if 25(OH)D < 50 nmol/L and 25000 UI/wk if 25(OH)D < 75 nmol/L aiming at improved immunologic recovery with reduced levels of inflammation, immune activation, and increased immunity against pathogens[43].

The COVID-19 pandemic presents a puzzling challenge without specific treatment yet with timely administration being crucial for all current regimens on clinical trial or use. This is also the case for vitamin D, and this might be the reason why in a recent RCT, a single enteral dose of 540000 IU of vitamin D3 or matched placebo started late within 12 h after the decision to admit the critically ill (unrelated to COVID- 19) vitamin D deficient patient to an intensive care unit, had no benefit at a 90-d all-cause, all-location mortality[44]. Regarding vitamin D, we know that respiratory viruses downregulate vitamin D receptor expression in human bronchial epithelial cells, while improvement in vitamin D status increases antiviral defenses *via* cathelicidins and innate interferon pathways[45]. Vitamin D has a 12% overall protective effect against bacterial and viral acute respiratory tract infection, increased to 19% in those individuals on daily or weekly regimen compared to those on monthly boluses and up to 70% when vitamin D deficiency is corrected with daily supplementation[46]. Bioavailable 25(OH)D is inversely associated with illness severity in critically ill ICU patients associated with increased mortality and morbidity[47]. Calcitriol [1,25$(OH)_2D_3$] alleviates lipopolysaccharide induced acute lung injury and prevents the adult respiratory distress syndrome by minimizing the alveolar damage[48]. Vitamin D is also a negative endocrine regulator of the renin-angiotensin system. The mechanism for SARS-CoV-2 infection is the requisite binding of the virus to the membrane-bound form of ACE2 and internalization of the complex by the host cell. Recognition that ACE2 is the main host receptor by SARS-CoV-2 to infect human has prompted new therapeutic approaches to block the enzyme or reduce its expression to prevent cellular entry of SARS-CoV-2 in tissues expressing ACE2 (lung, heart, kidney, brain, and gut). Thus, it seems that both stimulation of the immune system and inhibition of renin-angiotensin system are mechanisms by which vitamin D may play a beneficial role in COVID-19 infection[49]. Vitamin D repletion in critical illness with a more aggressive dosing is showing similarly promising results with vitamin C repletion in septic shock[50] and may be able to prevent the cytokine storm that seems to be killing people rather than the virus itself[51]. C-reactive protein is a surrogate marker for unregulated inflammation and cytokine storm and is associated with vitamin D deficiency. Retrospective data and indirect evidence also show a possible role for vitamin D in reducing complications attributed to and the cytokine storm itself[52]. Moreover, recent research revealed that vitamin D receptor signaling in macrophages regulates a shift between proinflammatory and anti-inflammatory activation during ER stress-induced inflammation[53]. Thus, supplementation within recommended upper safety limits, for specific nutrients such as vitamins C and D, warrants optimal nutritional status to insure a well-functioning immune system protecting against viral infections[54].

Recent research demonstrated that low serum 25(OH)D was an independent risk factor for COVID-19 infection and hospitalization analyzing data from 14,000 members of Leumit Health Services in Israel[55]. A very recent pilot randomized clinical study demonstrated that administration of a relatively high dose (0.532 mg-21280 IU) of calcifediol or 25(OH)D, followed by 0.266 mg on days 3 and 7, and then weekly until discharge or ICU admission, significantly reduced the need for ICU treatment of patients requiring hospitalization due to proven COVID-19 disease[56]. In a single-center, retrospective cohort study concerning 489 patients, likely deficient vitamin D status was associated with increased COVID-19 risk[57].

Our analysis took place at two completely different time points during the beginning and the end of the first wave of this pandemic. We needed to confirm our first results at a completely different time point of the first wave. One could not attempt to extend this type of approach to the second wave or the third wave, which is now hitting Europe, first because the virus has significantly spread into the European populations. Secondly, after extended lockdowns and limited - if any - summer vacations and with no public health authority having officially advised supplementation with vitamin D even aiming to protect musculoskeletal health, one can hypothesize that the European population vitamin D status had to be worse, and this could also be one of the main reasons why the second and third waves appeared more

deadly than the first, at least in several European countries, even in sunny countries as Greece. One of the main outcomes of our analysis though is that vitamin D does not prevent SARS-CoV-2 from spreading, while it may protect from serious-critical illness and death form COVID-19 disease, with significant and substantial protection being obtained at a 25(OH)D concentration of 100-150 nmol/L (40-60 ng/mL).

CONCLUSION

At this time and despite the ongoing debate on "The Big Vitamin D Mistake"[15], referring to the statistical error in the estimation of the Recommended Dietary Allowance of vitamin D discovered by Veugelers and Ekwaru[58] in 2014 and confirmed by Heaney *et al*[59]: About 4000 IU/d (3385) are needed to ensure 50 nmol/L in 97.5% of the population, about 6000 IU/d (6201) are needed to achieve the Endocrine Society's recommendation of 75 nmol/L and about 9000 IU/d (9122) to reach 100 nmol/L, and even if the vitamin D deficiency pandemic is still being questioned[60], no one should confuse the global consensus on the minimum vitamin D doses needed to prevent nutritional rickets[61], with the doses needed to exert all of its extra-skeletal health benefits[62], particularly those related to our immune system. Apart from the known disagreement between the Endocrine Society and the Institute of Medicine (IOM) but also the discrepancy between the IOM and the Scientific Advisory Committee on Nutrition in Great Britain, two equally respectable government advisory committees, who after reviewing the same evidence, ended up with a twofold difference in target concentrations in serum 25(OH)D and similarly divergent conclusions for intakes of vitamin D[12], one can notice that differences concerning upper tolerable limits for vitamin D administration are limited. The more conservative IOM advises up to (upper tolerable limit) 1500 IU daily in infants < 1 year, 2500 IU in children 1-3 years, 3000 IU in children 4-8 years and up to 4000 IU for everybody after 9 years of age; where the Endocrine Society advices are up to 2000 IU for infants < 2 years, up to 4000 IU for children 1-18 years and up to 10000 IU for adults, adult pregnant and lactating women as well as the elderly, underlining that obese people may need up to two to three times more, as it may be needed to correct vitamin D deficiency or to treat specific conditions such as rickets, osteomalacia, hyperparathyroidism, malabsorption syndromes or if on medications affecting vitamin D's metabolism. However, the doses that the Endocrine Society practice committee characterizes as not requiring medical supervision are practically identical to the IOM's upper tolerable limits. Thus, supplementation with vitamin D within recommended safety limits, with doses that do not require prior measurement of the 25(OH)D concentration or medical supervision, apart from the already established protective role in bone mineral density[63], may also assure a well-functioning immune system[64].

In 2011, the Endocrine Society published the Endocrine Society Practice Guidelines on vitamin D, recommending how to treat and prevent vitamin D deficiency in children and adults. Based on the literature these recommendations were related to maximizing musculoskeletal health. However, in 2011 there was not enough scientific evidence for the Committee to recommend improvement in vitamin D status for reducing risk of many chronic illnesses or improving immune function. During the past decade, however, numerous studies have been conducted demonstrating that improvement in vitamin D status reduces risk for upper respiratory tract viral infections as well as having a wide variety of effects on both innate and acquired immunity[39,65]. A recent randomized controlled double-blind clinical trial assessed the impact of vitamin D supplementation on calcium metabolism and non-calcemic broad gene expression by relating them to the individual's responsiveness to varying doses of vitamin D3[66]. Thirty healthy adults were randomized to receive 600, 4000 or 10000 IU/d of vitamin D3 for 6 mo. Circulating parathyroid hormone (PTH), 25(OH)D, calcium and peripheral white blood cells broad gene expression were evaluated. The investigators reported dose-dependent increase in circulating 25(OH)D concentrations, decreased PTH concentrations and no change in serum calcium levels. A plateau in circulating PTH levels was achieved at 16 wk in the 4000 and 10000 IU/d groups. There was a dose-dependent 25(OH)D alteration in broad gene expression with 162, 320 and 1289 genes up- or down-regulated in their white blood cells, respectively. Thus, improvement in vitamin D status does have a dramatic effect on immune cell activity. However, can it therefore be expected that everyone who improves their vitamin D status would experience the same genomic influences on their immune system if they raised their blood level of 25(OH)D to the same degree? Carlberg and

Haq[67] gave daily 3200 IU of vitamin D3 to 71 prediabetic patients for 5 mo and found robust changes in total gene expression in peripheral blood mononuclear cells only in about half the subjects. Shirvani *et al*[66] observed in healthy adults who were vitamin D deficient and who received this same dose of vitamin D and raised their blood concentrations of 25(OH)D to the same degree, marked differences in the level of expression of the same genes. They reported that 60% of the healthy vitamin D deficient adults who received 10000 IU daily for 6 mo had a robust response in gene expression compared to the other 40% who had minimum to modest responses even though these subjects raised their blood concentrations of 25(OH)D in the same range of 60-90 ng/mL (150-225 nmol/L).

With all of this compelling information, it is reasonable for all responsible Public Health Authorities to consider advising their populations to enhance their immune system by improving their vitamin D status by encouraging sensible sun exposure and by taking vitamin D supplements (if not already on adequate supplementation or medically prohibited due to a vitamin D hypersensitivity disorder) at the doses which, as proposed by the Endocrine Society Guideline Committee in 2011, do not require previous laboratory testing nor medical supervision. To prevent nutritional rickets, daily doses of 400-1000 IU in infants, 600-1000 in children and 1500-2000 in teenagers (should be treated as adults) and adults, are needed. However, to achieve higher circulating concentrations of 25(OH)D at the range of 100-150 nmol/L (40-60 ng/ml), appearing according to our analysis to be necessary for substantially improving immune function and protect from COVID-19 disease, without any risk of toxicity[68], higher doses can be used. As mentioned above, the Endocrine Society Practice Guidelines recommends the safe upper limit for infants < 1 year is 2000 IU daily, children 1-18 years 4000 and adults (including elderly and adult pregnant-lactating women) 10000 IU, unless they are obese, requiring two to three times more. Thus, after a necessary initial repletion for up to 2 mo with these upper tolerable doses, the Endocrine Society's Committee's maintenance proposed doses, which can be safely given without medical supervision to prevent vitamin D deficiency and are practically identical with the IOM's upper tolerable limits, can be continued: *i.e.* up to 1000 IU/d for infants aged < 6 m, 1500 for age 6 m - 1 year, 2500 for 1-3 years, 3000 for children 4-8 years and 4000 for children > 8 years, with adults, pregnant/lactating women and adolescents requiring a daily intake of 4000-5000 (8000-10000 if obese) to maintain circulating concentrations of 25(OH)D at the range of 100-150 nmol/L. For teenagers and adults on a weekly scheme, these doses translate to about 50000 or if obese 100,000 IU, this being equivalent to approximately 6000 IU daily and 12000 IU for obese, respectively.

These doses will achieve blood concentrations of 25(OH)D of at least 75 nmol/L (30 ng/mL) aiming at the preferred range of 100-150 nmol/L (40-60 ng/mL), without any risk of toxicity[68]. It has been estimated that once a blood concentration of 25(OH)D reaches 50 nmol/L (20 ng/mL) that for every 100 IU ingested, the blood concentration increases by approximately 0.6-1 ng/mL. A good example of this dosing was reported by Shirvani *et al*[66] who demonstrated that circulating concentrations of 25(OH)D were maintained in the range of 24.3 ± 4.1, 40.8 ± 3.8 and 78.6 ± 13.5 ng/mL, in vitamin D deficient adults who ingested 600, 4000 and 10000 IU daily for 6 mo. These data are supported by a population based Canadian study demonstrating that some adults taking up to 20000 IU daily for more than a year maintained a blood concentration of 25(OH)D in the range of 60-80 ng/mL without any evidence of toxicity[69]. This study also nicely demonstrated the effect of BMI on vitamin D status. The authors observed that those who had a BMI > 30 kg/m^2 needed to ingest 2.5 times more vitamin D to maintain the same blood level as a normal weight adult.

Achieving circulating concentrations of 25(OH)D in the range of 100-150 nmol/L (40-60 ng/mL) appears to optimize vitamin D's effect on improving immune function, thereby substantially reducing the risk for serious-critical infections, particularly from SARS-CoV-2 according to our study, and possibly modulating the immune response, helping to prevent the dangerous cytokine storm often leading to COVID-19 related deaths. The COVID-19 pandemic is an unprecedented medical emergency for the modern world, and we may not possess the luxury, the time nor even the ethical argument to wait the definite results on RCTs while people are dying[70], while prospective well designed studies are needed to conclude on the impact of the vitamin D status on COVID-19 morbidity and mortality[71]. These trials are hopefully awaited, but before a medical emergency of this magnitude we need to remember that Evidence Based Medicine is not necessarily synonymous to RCTs. We do know that vitamin D enhances immune function. We know the extent of vitamin D deficiency, and we know that restrictions and lockdowns have probably worsened the populations' vitamin D status. Thus, until then, decisions are taken based on and adapted to the best available

evidence. And, as far as vitamin D, the evidence is there[51], justifying even the use of vitamin D as a possible adjuvant therapy for COVID-19 disease[72]. A preponderance of evidence does suggest that vitamin D deficiency increases mortality. Our findings predict a striking reduction of serious-critical illness and deaths from COVID-19 if 25(OH)D concentrations reach 100-150 nmol/L (40-60 ng/ml), and very recently SARS-CoV-2 positivity was found to be strongly and inversely associated with circulating 25(OH)D concentrations irrespective of latitudes, races/ethnicities, both sexes and age ranges[73]. Slovakia, at five deaths/M, having the lowest mortality rate in Europe from COVID-19 disease at the time of our analysis, a 125-fold lower than in the UK where official advice remains that 25(OH)D deficiency is < 25 nmol/L (https://www.nice.org.uk/advice/es28/evidence/evidence-review-pdf-8777674477), is a characteristic paradigm, being practically the only country in Europe with a 25(OH)D status meeting the Endocrine Society's recommended level of sufficiency > 75 nmol/L (30 ng/mL).

From a public health perspective, given the established safety of even high doses, and the potential benefits in enhancing innate and adaptive immunity[74], mitigating also the inflammatory response[3], the recommendation of intensive supplementation with vitamin D as possible prophylaxis with safe doses that do not require prior measurement or medical supervision, must be seriously considered, especially now that the world is facing the third deadly wave of this pandemic, forcing populations into repeated new lockdowns without the broad availability of specific medications yet and while awaiting for vaccinations to be widely available and plausible.

There is no need to require a measurement of serum 25(OH)D before recommending treatment and/or supplementation with vitamin D. This is supported by the observation that ingesting 50000 IU of vitamin D every 2 wk for up to 6 years is not associated with any toxicity[75]. Furthermore, this study was conducted in a clinical setting and all patients were prescribed this vitamin D therapy without the knowledge of their baseline serum 25(OH)D concentration. After completion of the study, the baseline levels were measured. Some of the patient's had a blood concentration of 25(OH)D of 125 nmol/L (50 ng/mL) and after being on 50000 IU of vitamin D once every 2 wk, their 25(OH)D concentration reached 200 nmol/L (80 ng/mL) without any evidence of toxicity[75].

There is essentially no vitamin D naturally occurring in the diet apart from oily fish, cod liver oil and sun-dried mushrooms. The modern way of life deprives us from sun exposure together with the warning to avoid all direct sun exposure by the national and international Dermatology Societies contributing to the worldwide vitamin D deficiency pandemic: Approximately 40% of the world's population is vitamin D deficient, *i.e.* 25(OH)D < 50 nmol/L (20 ng/mL) and 60% or insufficient *i.e.* 50-79 nmol/L (20-29 ng/mL). Therefore, we also need to consider worldwide recommendations for vitamin D food fortification that is practiced in several countries including the United States, Canada, and Finland to name a few. Most other countries either do not encourage or forbid food fortification with vitamin D. Recently, in 2017, India implemented fortification of milk and cooking oil with vitamin D2 as a means of reducing vitamin D deficiency that is common in both children and adults in this sunny Asian subcontinent.

Vitamin D is safe, not toxic and inexpensive. In the "shade" of the modern way of life, the human body cannot produce enough vitamin D from sun exposure, as our hunter gatherer forefathers did and as Maasai herders and the Hazda continue to do. Vitamin D may improve and modulate immune response against SARS-CoV-2. With all the above data, the limitations and the perspectives discussed, the possible benefit in the fight against SARS-CoV-2 should the protection against COVID-19 serious-critical illnesses and death with vitamin D prove truthful, and this without any risk of toxicity, the gain for humanity as well global public health might be just invaluable.

ARTICLE HIGHLIGHTS

Research background

Recent studies have claimed lower coronavirus disease 2019 (COVID-19) cases in European countries with a better vitamin D status and a significant association between vitamin D sufficiency and reduction in clinical severity and inpatient mortality from COVID-19 disease. Low serum 25(OH)D was identified as an independent risk factor for COVID-19 infection and hospitalization, and administration of calcifediol or 25(OH)D significantly reduced the need for intensive care unit treatment.

Research motivation

Vitamin D population status may indeed have possible unappreciated consequences to the COVID-19 pandemic, a hypothesis that needed to be further elucidated.

Research objectives

Following an ecological integrative approach, we examined the associations between published representative and standardized European population vitamin D data and the Worldometer COVID-19 data at two completely different time points of the first wave of this pandemic. If any sustained correlations were to be found, they would be an indication of a truthful association, even though they could not prove causality.

Research methods

Using linear regression, we explored the correlation between published representative and standardized population vitamin D concentrations and the number of total cases/million (M), recovered/M, deaths/M and serious-critically ill/M from COVID-19 for 26 European countries populated > 4 M. Life expectancy (LE) was also analyzed with semi-parametric regression. Weighted analysis of variance/analysis of covariance evaluated serious-critical/M and deaths/M by the vitamin D population status: deficient < 50, insufficient: 50-62.5, mildly insufficient > 62.5-75 and sufficient > 75 nmol/L, while controlling for LE for deaths/M. Statistical analyses were performed in XLSTAT LIFE SCIENCE and R (SemiPar library).

Research results

No correlation was found between population vitamin D concentrations and the total cases-recovered/M, but negative correlations were depicted predicting a reduction of 47%-64%-80% in serious-critical illnesses/M and of 61%-82%-102.4% in deaths/M, further enhanced when adapting for LE by 133%-177%-221% if 25(OH)D concentrations reach 100-125-150 nmol/L. Weighted analysis of variance evaluated serious-critical/M ($r^2 = 0.22$) by the vitamin-D population status and analysis of covariance the deaths/M ($r^2 = 0.629$) while controlling for LE ($r^2 = 0.47$). Serious-critical showed a decreasing trend ($P < 0.001$) from population status deficient ($P < 0.001$) to insufficient by 9.2% ($P < 0.001$), to mildly insufficient by 47.6% ($P = 0.044$) and to sufficient by 100% (reference, $P < 0.001$). For deaths/M the respective decreasing trend ($P < 0.001$) was 62.9% from deficient to insufficient ($P < 0.001$), 65.15% to mildly insufficient ($P < 0.001$) and 78.8% to sufficient ($P = 0.041$).

Research conclusions

A higher 25(OH)D concentration may protect from serious-critical illness and death from COVID-19 disease - even more in the elderly - but does not seem to prevent severe acute respiratory syndrome coronavirus 2 from spreading.

Research perspectives

Considering the ongoing pandemic situation, the presented results are useful for public health systems to advise their populations to enhance their immune system by improving their vitamin D status. Specifically, achieving a serum 25(OH)D concentration of 100-150 nmol/L (40-60 ng/mL) with vitamin D2/D3 supplementation using the upper tolerable daily doses for up to 2 mo (infants < 1 year 2000 IU daily, children 1-18 years 4000 and adults including elderly and adult pregnant-lactating women 10000 IU, unless they are obese requiring 2-3 times more) followed by the maintenance proposed doses not requiring medical supervision, as proposed by the Endocrine Society and being practically identical with the Institute of Medicine's upper tolerable limits (up to 1000 IU/d for infants aged < 6 mo, 1500 for age 6 mo - 1 year, 2500 for 1-3 years, 3000 for children 4-8 years and 4000 IU for children > 8 years, with adults, pregnant-lactating women and adolescents requiring a daily intake of 4000-5000 unless they are obese requiring two to three times more) may protect from serious-critical illness and death from COVID-19 disease.

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CASE REPORT

Chest radiography requirements for patients with asymptomatic COVID-19 undergoing coronary artery bypass surgery: Three case reports

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Abstract

BACKGROUND

The coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus-2, represents a major challenge to health care systems both globally and regionally, with many opting by cancelling elective surgeries. Cardiac operations in patients diagnosed with COVID-19 have been imperative due to their emergency nature, critical condition of patients awaiting cardiac surgery, and accumulated number of cardiac surgical interventions throughout the last months.

CASE SUMMARY

Here we describe three COVID-19 positive cases who underwent coronary surgery, on an urgent basis. We did not experience worsening of the patients' clinical condition due to COVID-19 and therefore a routine post-operative chest X-ray (CXR) was not required. None of the health care providers attending the patients endured cross infection. Further trials would be needed in order to confirm these results.

CONCLUSION

While the pandemic has adversely hit the health systems worldwide, cardiac surgical patients who concomitantly contracted COVID-19 may undergo a smooth post-operative course as a routine post-operative CXR may not be required.

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Core Tip: Routine chest radiology is considered one of the core components of the post-operative care in cardiac surgery settings, there may be additional benefits in patients with associated coronavirus disease 2019 (COVID-19) infection to check the possible lung involvement. However, we found that routine chest radiology may not be required for post-operative care in COVID-19 patients undergoing cardiac surgery. This may reduce overall costs and radiographer's unnecessary exposure.

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INTRODUCTION

The World Health Organization (WHO) declared the coronavirus disease 2019 (COVID-19) as a global pandemic in March 2020, after the disease swept across the world from its epicenter in Wuhan, China. The disease represented a major challenge for the public and healthcare community globally[1]. The pandemic overwhelmed the health systems, forcing major changes in the health care practices[2]. Under the pressure from acute bed shortage, many health care facilities opted to defer elective surgical procedures[3], consequently, cardiac surgery elective services were forced to be canceled or postponed[4]. Shoman *et al*[5] reported that urgent cardiac in patients with COVID-19 without pneumonia could be carried out safely without further complications or health care associated cross infection, if strict infection control protocols would be enforced during the procedure[5].

The explosive and uncontrolled spread of COVID-19 globally made it imperative for the cardiac surgery societies to release guidelines and protocols aiming to risk assess protocols based on probabilities and resources[6]. Here we describe three COVID-19 positive cases, with no pulmonary-related symptoms, diagnosed with significant coronary artery disease and subsequently subjected to urgent coronary surgery. This manuscript also sheds light on the role of routine chest radiology in perioperative management.

CASE PRESENTATION

Chief complaints

Case 1: A 43-year-old gentleman was presented to the hospital with recent onset chest pain.

Case 2: A 50-year-old gentleman was presented to the emergency cardiac department with acute onset of severe chest pain.

Case 3: A 47-year-old gentleman came to the emergency room with typical post-prandial chest pain.

History of present illness

Case 1: The patient's 12-lead electrocardiogram (ECG) indicated a non-ST segment elevation myocardial infarction (NSTEMI). Subsequent coronary angiography revealed critical left main coronary artery distal occlusion with additional three vessels coronary artery disease (CAD), all of which were severely occluded.

Case 2: The patient's 12-lead ECG showed anterior wall ST segment elevation myocardial infarction (STEMI). Subsequent coronary angiography revealed left main coronary artery disease, left anterior descending, and left circumflex coronary artery disease. Patient's routine swab was positive for COVID-19, but no respiratory symptoms noted. Chest radiology was normal.

Case 3: The working diagnosis after evaluating his 12-ECG was NSTEMI. Coronary angiography detected significant three vessels CAD and patient was referred for urgent surgical revascularization.

History of past illness

Case 1: Patient's past medical history included type II-diabetes mellitus, smoking, and dyslipidemia.

Case 2: Unremarkable past medical history.

Case 3: Patient's medical history was significant for diabetes mellitus, hypertension, smoking, and dyslipidemia.

Physical examination

Case 1: None.

Case 2: The patient's pre-procedure examination was unremarkable. The vital signs showed temperature of 37.1 °C, blood pressure of 127/77 mmHg, heart rate of 87 beats/min regular, and oxygen saturation of 98% on supplemental oxygen flow at 2 liters/min delivered *via* nasal cannula.

Case 3: The patient pre-procedure examination was unremarkable. The vital signs showed temperature of 36.8 °C, blood pressure of 107/67 mmHg, heart rate of 77 beats/min regular, and oxygen saturation of 97% on room air.

Laboratory examinations

Case 1: Routine nasopharyngeal swab was positive for COVID-19 after admission, without respiratory symptoms or chest roentgenogram findings.

Case 2: Patient's routine swab was positive for COVID-19, no respiratory symptoms noted, and normal chest radiology.

Case 3: Similar to the previous two patients here studied, a positive swab for COVID-19 was taken, without additional clinical or radiologic manifestations.

FINAL DIAGNOSIS

Cases 1 and 3: Acute NSTEMI with three vessels disease. Patient positive for COVID-19.

Case 2: Acute STEMI with three vessel disease. Patient positive for COVID-19.

TREATMENT

Case 1: The patient subsequently underwent urgent surgical revascularization with three grafts. Full personal protective equipment (PPE) was used, with the anesthesia team taking a lead in the operating room team preparation and theatre. Patient followed a dedicated predesigned transport from and to the operating room and the cardiothoracic intensive care unit (ICU) for post-operative recovery.

Case 2: Patient underwent urgent surgical revascularization under the departmental predesigned guidelines for surgical management of COVID-19 patients. Post-operatively, patient's disposition was carried out in an isolation room of the cardio-thoracic ICU (CTICU) and extubated within six hours of admission on the same day.

Case 3: Patient underwent on-pump coronary artery bypass graft and the procedure was uneventful.

OUTCOME AND FOLLOW-UP

Case 1: Patient's post-operative course in the CTICU was uneventful, after removal of the chest drain patient was discharged to the dedicated COVID-19 high dependency unit within the hospital for a short stay, in order to optimize COVID treatment. Patient was subsequently discharged home on the seventh post-operative day.

Case 2: The patient remained in the unit until removal of the chest drain and then transferred to the dedicated isolation ward in the hospital. Later, the patient was discharged home for self-quarantine, on the eight post-operative day, and subsequently followed up by routine telephonic consultation without any reported surgical complications.

Case 3: Patient was extubated on the same operative day in the CTICU and transferred to an isolation room on the ward in the first post-operative day, where cardiac rehabilitation was completed. Patient was then discharged for self-quarantine for 14 d.

No chest radiography was required in the aforementioned three patients (Table 1).

DISCUSSION

The challenge of handling urgent surgeries alongside COVID-19 diagnosis is of limited familiarity amongst practitioners. Decision making and risk assessment protocols can define COVID-19's influence on cardiothoracic surgical outcomes. The three patients here referred are examples of patients who had been through pragmatic decision making protocols to perform such surgeries. The apparent medical stability of these patients, from a respiratory standpoint, encouraged our team to act towards treating the patient's acute coronary syndrome, reducing possible related mortality and morbidity.

Anticipating the need to operate COVID-19 patients, our department developed a protocol for perioperative management of COVID-19 patients undergoing cardiac surgery, which was reviewed by all stakeholders. Furthermore, our team followed patients with COVID-19 after cardiac surgery with a chest radiology when clinically indicated as per the CTICU protocol. This was successfully carried out for all three patients here reported, without any significant clinical issue compromising the patient's outcome.

Triaging and routine testing

Reducing unnecessary chest radiology is a widely agreed goal in the post-operative care of patients after cardiac surgery. Tolsma *et al*[7] made an observational study with 1102 patients aiming to define clear indications for chest X-ray (CXR) after cardiac surgery. This practice was safe and effective in reducing the total number of CXRs performed and also anticipated increased efficacy[7]. Similarly, Forouzannia *et al*[8] reviewed 118 patients who underwent off pump coronary surgeries and their post-operative outcome did not change when CXR were eliminated in the post-operative period[8].

In our organization, we have defined certain criteria for chest radiography during post-operative cardiac surgical care. This included clinical evaluation-based findings of fever, dyspnea, abnormal pulmonary sounds, signs and symptoms of cardiac tamponade, abnormal chest tube bleed or air leak, and doubtful position of endodontically treated teeth and vascular lines. Hypoxia on pulse oximeter (SaO_2 < 92% on regular oxygen therapy) and multiple punctures during central venous access also mandated CXR. A final clinical evaluation focused on X-ray findings. All patients were discharged 5-7 d after surgery. A 30-d follow-up included at least two visits. Patients were in constant contact with the cardiac clinic. Symptomatic patients were selectively re-examined to rule out complications.

Decision to operate

In our tertiary center, we have set up a multidisciplinary team approach before deciding to surgically operate on COVID-19 positive patients. This team involved anesthesiologists, cardiac surgeons, cardiologists, and infectious diseases specialists. Asymptomatic but serologically positive COVID-19 patients underwent management as actively infectious. To all these patients the used of full PPE was mandatory[9]. The coronary lesions' anatomical complexity in all three patients here studied were treated as meaningful and consequently conceived to be subjected to operation. Significant left main disease or acute coronary syndrome not amenable to percutaneous intervention

Table 1 Description and outcome of the studied patients

	Case 1	Case 2	Case 3
Age	43	50	47
BMI (kg/m^2)	27.4	24.7	27.1
Creatinine (micromole/L)	97	64	81
EF%	62	57	58
Additive European score	0.68%	0.8%	0.68%
CPB time (min)	86	75	85
ACC time (min)	43	30	48
Anesthesia time (min)	287	280	245
VIS	13	5	8
LOS_{ICU} (h)	49	22	18
LOV (min)	707	722	505
LOS_{hosp} (d)	18	18	22
POAF	None	None	None
AKI	None	None	None
In-hospital-mortality	None	None	None
VA-ECMO	None	None	None
Re-admission ICU	None	None	None
Re-exploration	None	None	None
PMI	None	None	None
Pulmonary complications	None	None	None
Thromoembolic complications	None	None	None
Post-operative CXR requirement	None	None	None

ACC: Aortic cross clamp; AKI: Acute kidney injury; BMI: Body mass index; CXR: Chest X-ray; CPB: Cardiopulmonary bypass; EF: Ejection fraction; $LOS_{ICU:}$ Length of stay in intensive care unit; LOV: Length of mechanical ventilation; LOS_{hosp}: Hospital length of stay; PMI: Perioperative myocardial infarction; POAF: Post-operative atrial fibrillation; VA-ECMO: Venoarterial extracorporeal membrane oxygenation; VIS: Vasoactive inotrope score; ICU: Intensive care unit.

was a prerequisite for urgent or emergent surgical intervention[10].

Practice of routine post-operative chest radiograph

Most cardiac cardiothoracic centers practice CXR in the immediate post-operative period routinely, in absence of any clinical or laboratory indication. However, the accuracy of CXR in diagnosing pulmonary opacities in the post-operative period is limited and its accuracy in visualizing and defining etiology of pulmonary opacity is moderate[11]. Moreover, management may not be changed in response to abnormal CXR findings[12]. The risks associated with radiation exposure, manpower wastage, cost incurred, possible displacement of invasive line, and endotracheal tubes are additional concerns[13].

Transport and ICU disposition

We appealed the CTICU team to be present at the operating theatre door for receiving the patient and to minimize practitioners' transportability of a possibly contaminated PPE. Patient's transfer to the CTICU after surgery was carried out with a transport ventilator and minimal essential team comprised of a single respiratory therapist, nurse, and physician. Patel *et al*[14] emphasized the value of minimal ventilator circuit interruption, reducing practitioners' presence and unnecessary ventilator transport[14]. The same principles applied when attempting to do CXRs.

The patient's preparation before transport to ICU, by covering the patient with a plastic sheet and connecting them to a portable ventilator, was done after clamping/

de-clamping technique. Patient's escorting to the isolation room of the CTICU was done by the ICU team which comprised a physician, nurse, and respiratory therapist. Doffing of the anesthesia team was done in a pre-designated area in the operation theatre. The operation room was disinfected thereof and restricted until the following morning. The protocol for managing COVID-19 positive patients was followed by the anesthesia team.

The safety of patients transported to and from the theatres needs to be customized for each hospital, considering the basic principles of minimizing exposure and maximizing communication[15]. We have transferred COVID-19 positive patients to a COVID ICU unit enclosing negative-pressure rooms with additional high-efficiency particulate air filters. We have also taken into account early possible surgical complications such as arrhythmias, myocardial injury, acute renal injury, and the respiratory complications[16,17]. None of our three patients showed early cardiac or respiratory complications and all were able to be transferred from ICU after a median of 24 h after surgery.

CONCLUSION

While the pandemic adversely has hit the health systems worldwide, cardiac surgical patients who concomitantly contracted COVID-19 infection may undergo a smooth post-operative course as a routine post-operative CXR may not be required.

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