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Review

COMMON VARIABLE IMMUNODEFICIENCY: PREDISPOSING OR PROTECTIVE FACTOR FOR SEVERE COMPLICATIONS OF COVID-19?

Thomas Ferenc[1] and Tatjana Vilibić-Čavlek[2,3]

[1]Department of Diagnostic and Interventional Radiology, Merkur University Hospital, Zagreb, Croatia;
[2]School of Medicine, University of Zagreb, Zagreb, Croatia;
[3]Department of Virology, Croatian Institute of Public Health, Zagreb, Croatia

SUMMARY – Coronavirus disease 2019 (COVID-19) is an emerging infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The usual presentation of the disease is a common cold-like illness but it can present with more severe and sometimes fatal manifestations. Immunocompromised patients such as those with common variable immunodeficiency (CVID) also are among the infected population. A limited number of reports have been published concerning CVID patients with COVID-19. The main reported symptoms were fever, cough, dyspnea and fatigue while the median duration of illness was 19 (interquartile range 14-26.5) days. Total recovery rate was 88.4%. It is still unknown whether primary immunodeficiency interacts as a predisposing or protective factor against the severe forms of COVID-19. Substitute immunoglobulin (IG) therapy is the only treatment option for CVID. Some reports suggest that early administration of intravenous IGs or convalescent plasma infusion may positively influence the outcome of COVID-19 in these patients.

Key words: *Common variable immunodeficiency; COVID-19; SARS-CoV-2*

Introduction

Coronavirus disease 2019 (COVID-19) is an emerging respiratory infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The origin of COVID-19 outbreak was in Wuhan City, China, in December 2019 and the World Health Organization (WHO) formally declared it a pandemic in March 2020. Since then, SARS-CoV-2 infected more than 167 million people and caused approximately 3.5 million deaths[1]. SARS-CoV-2 is an enveloped RNA virus that belongs to the family *Coronaviridae* and is the seventh known member of the family that is capable of infecting humans[2]. There are several documented modes of transmission with evidence supporting respiratory and airborne as the main modes[3]. Clinical features of COVID-19 vary from asymptomatic or mild common cold-like symptoms (81%) to more severe manifestations such as severe respiratory failure (14%) and critical illness (5%)[2,4]. Rapid replication of SARS-CoV-2 may generate strong immune response, which often results in development of cytokine storm syndrome, acute respiratory

Correspondence to: *Thomas Ferenc, MD*, Department of Diagnostic and Interventional Radiology, Merkur University Hospital, Zajčeva 19, HR-10000 Zagreb, Croatia
E-mail: thomas.ferenc95@gmail.com
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distress syndrome (ARDS) and respiratory failure. The latter is often considered the main cause of death in patients with COVID-19[4]. Common variable immunodeficiency (CVID) is a primary immunodeficiency that is characterized by insufficient immunoglobulin (IG) production and reduced serum levels of immunoglobulin G (IgG), immunoglobulin M (IgM) and/or immunoglobulin A (IgA)[5]. CVID patients mostly present with recurrent sinopulmonary infections but there is also an association with autoimmune disorders, lymphoproliferative disorders, and an increased risk of developing malignancy. The association of COVID-19 with primary immunodeficiencies such as CVID is not sufficiently documented. The aim of this mini-review was to analyze reported cases and provide more epidemiological and clinical information on CVID patients with COVID-19.

Materials and Methods

Literature search was performed in PubMed, Medline, Google Scholar, ScienceDirect, Web of Science, Scopus and ClinicalKey, along with Google search with no limitations placed on the date and year of publication. The keywords used were "Common variable immunodeficiency", "COVID-19" and "SARS-CoV-2". Additional studies were identified by reviewing reference lists of retrieved studies. Restriction criterion was placed on the English-language articles only. After the list of studies was assembled, studies appearing to meet the inclusion criteria were reviewed in full and 44 studies were included.

Results

Until April 5, 2021, 17 studies were published regarding 70 CVID patients with COVID-19 (Table 1, Fig. 1). Their median age at the time of diagnosis was 44.5 (interquartile range (IQR) 33-59) years and 54% were males. The main symptoms reported in patients were fever (76.8%), cough (68.1%), dyspnea (40.6%) and fatigue (27.5%) while the median duration of illness was 19 (IQR 14-26.5) days. At the time of infection, 89.1% of patients were on regular CVID treatment and 91.8% of them recovered from COVID-19. Also, this study detected five cases of no regularity in IG application where full recovery was still accomplished. In 87.8% of cases, simultaneous co-infection did not develop but four patients had blood cultures, sputum, nasal secretion or bronchoscopy samples positive for bacteria and fungi (methicillin-resistant *Staphylococcus aureus* (MRSA), β-lactamase producing *Escherichia coli*; *Aspergillus* spp., *Streptococcus agalactiae*; *Enterococcus faecium*; and *Candida* spp., respectively). Admission to the intensive care unit (ICU) was required in 24.6% of patients and 11 of them recovered after ICU treatment. Total recovery rate was 88.4% and eight patients (seven females) passed away. Median age of the deceased patients was 56.5 years (IQR 51-63).

Discussion

The results of this review showed that median age of CVID patients at the time of COVID-19 diagnosis was 44.5 years. This differs from the general worldwide population where the reported median age at the time of infection was between 50 and 61 years[4,6,7]. Males were more susceptible to SARS-CoV-2 infection and the main symptoms (fever, cough, dyspnea and fatigue) correlated with the symptoms in immunocompetent persons[4,6]. One of the main CVID characteristics is increased susceptibility to recurrent and chronic infections. Encapsulated bacteria (e.g., *Streptococcus pneumoniae, Haemophilus influenzae*), fungi and viruses are frequent causes of various infections due to impaired antibody production in these patients. Moreover, there are reports that CVID patients are less prone to viral infections and mainly susceptible to rhinoviruses, herpesviruses and noroviruses[8]. Immune response to viral infections is usually activated at the cellular level after replication and consists of two main antiviral mechanisms including induction of interferons (IFN) and production of cytokines, and recruitment of specific white blood cells[9]. Primary proinflammatory cytokines are interleukin-1 (IL-1), interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α). The pathophysiological mechanisms of COVID-19 are still being researched but reduced IFN response and significant cytokine response to the virus was observed (mainly IL-1 and IL-6)[9,10]. Therefore, it seems that SARS-CoV-2 induces severe inflammatory response through macrophage activation, which leads to a cytokine storm[10-12]. Some authors even suggest COVID-19 hemoglobinopathy and resulting hypoxia as one of the leading causes of COVID-19 related ARDS[13]. CVID patients possess dysfunctional B-lymphocytes, which may contribute to poor cytokine response. Recent studies have shown that patients with primary immu-

Table 1. Epidemiological and clinical findings in CVID patients with COVID-19

Country	No. of patients	Age	Sex	Duration of COVID-19 symptoms (days)	Clinical symptoms at admission	Regular CVID treatment prior to COVID-19 infection	Co-pathogens	ICU admission	Outcome	Ref.
Belgium	1	37	M	47	Fever, cough, dyspnea, anorexia	Yes	None	Yes	Recovery	(32)
Brazil	3	25, ND, 27	2 M, 1 F	19, 2 ND	Fever, cough, dyspnea, anosmia, ageusia, parotiditis, diarrhea, night sweating	3 yes	3 none	1 yes, 2 no	3 recoveries	(31,38, 43)
Chile	1	ND	M	ND	Fever, GIS	Yes	None	No	Recovery	(38)
France	6	ND	4 M, 2 F	5 ND, 60	Fever, cough, dyspnea, fatigue, GIS, URS, myalgia	6 yes	6 none	6 no	6 recoveries	(38)
Italy	13	59, 32, 57, 52, 41, 8 ND	6 M, 7 F	20, 16, 25, 21, 19, 17, 7 ND	Fever, cough dyspnea, myalgia, URS, anosmia, chest pain, GIS	8 yes, 5 ND	6 none, 1 *Candida* spp., 1 bacterial pneumonia, 5 ND	7 yes, 6 no	11 recoveries, 2 deaths	(8,38)
Netherlands	1	40	F	41	Fever, cough, dyspnea, sore throat, chest pain, sinusitis	No	None	No	Recovery	(21)
Romania	1	ND	ND	ND	ND	ND	ND	ND	ND	(39)
Spain	6	6 ND	3 M, 3 F	17, 5 ND	AMS, fever, cough, sore throat, GIS, fatigue, dyspnea	6 yes	1 *E. faecium*, 5 none	6 no	5 recoveries, 1 death	(38)
UK	1	1 ND	M	ND	Fever, cough, myalgia, dyspnea, fatigue	Yes	Bacterial pneumonia	No	Recovery	(38)
USA	36	42, 82, 61, 38, 65, 38, 49, 56, 54, 76, 28, 33, 25, 41, 24, 68, 66, 45, 44, 20, 29, 59, 53, 53, 64, 59, 15, 9 ND	18 M, 18 F	30, 30, 19, 24, 41, 6, 10, 21, 29, 16, 28, 14, 11, 7, 7, 42, 16, 7, 7, 5, 17, 24, 14, 14, 12 ND	Fever, cough, dyspnea, diarrhea, chills, fatigue, weakness, headache, emesis, AMS, AP, anosmia, ageusia, sore throat, rash, anorexia, loss of appetite, dehydration, rhinorrhea, hemoptysis, abdominal distension, lethargy, nausea, vomiting, myalgia, chest pain, malaise, nasal congestion, URS, GIS	9 ND, 22 yes, 5 no;	15 ND; 19 none, 1 *MRSA, E. coli*; 1 *Aspergillus* spp., *S. agalactiae*	2ND, 8 yes, 26 no	31 recoveries, 5 deaths	(11,12, 20,24, 28, 35, 38, 40-42, 44)
ND	1	ND	M	ND	Fever, URS, myalgia	Yes	None	No	Recovery	(38)

CVID = common variable immunodeficiency; COVID-19 = coronavirus disease 2019; UK = United Kingdom; USA = United States of America; M = male; F = female; ICU = intensive care unit; Ref. = reference(s); MRSA = methicillin-resistant *Staphylococcus aureus*; AMS = altered mental status; AP = abdominal pain; GIS = gastrointestinal symptoms; URS = upper respiratory symptoms; ND = no data

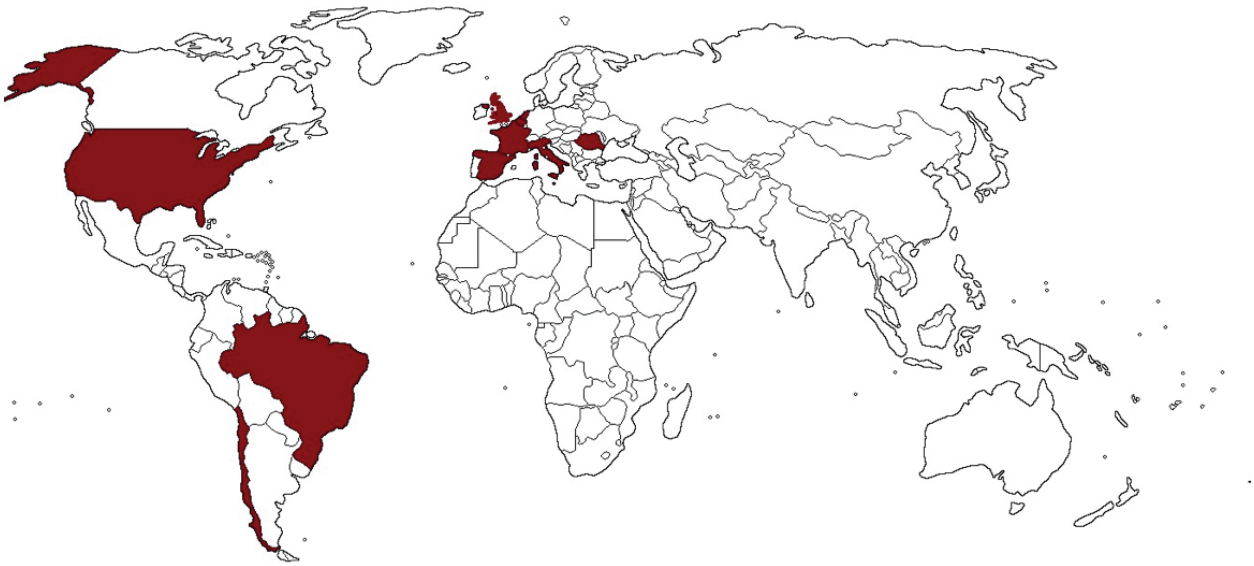

Fig. 1. Geographical distribution of reported cases of CVID patients with COVID-19.

CVID = common variable immunodeficiency; COVID-19 = coronavirus disease 2019

nodeficiencies have impaired IL-6 pathway, lacking expression of IL-6 receptors and subsequent unresponsiveness to IL-6[14,15]. Moreover, it has been documented that CVID presents with reduced functioning of specific toll-like receptor (TLR) pathway including TLR-7 (responds to RNA viruses)[16] and TLR-9. These receptors are important in antiviral response and proinflammatory cytokine production[17]. Abraham *et al.*[18] have shown that impaired function of B-lymphocytes or low IG levels in immunocompromised COVID-19 patients may not necessarily predict high mortality rates but they may imply an increase in morbidity. Quinti *et al.*[8] found that SARS-CoV-2 positive CVID patients presented with more severe form of the disease in contrast to patients with agammaglobulinemia, which suggests that B-lymphocytes play a certain role in SARS-CoV-2 induced inflammation. Nguyen *et al.*[19] also suggest that antibodies or B-lymphocytes may exacerbate the course of COVID-19. In comparison to Quinti *et al.*[8], the CVID cohort in the study by Cohen *et al.*[20] presented with higher recovery rates and milder course of COVID-19. Despite dysfunctional B-lymphocytes and the inability to produce antibodies, it was shown that CVID patients may develop SARS-COV-2 IgM and IgG antibodies seven weeks after the first symptoms[21].

Data on T-cell response in COVID-19 are limited but Grifoni *et al.*[22] detected SARS-CoV-2-reactive $CD4^+$ T-cells in 40%-60% of unexposed healthy persons, which assumes cross-reactive T cell reaction between SARS-CoV-2 and other human coronaviruses (HCoV). A similar study was conducted by Steiner *et al.*[23], where the authors evaluated T-cell responses to SARS-CoV-2 and two strains of HCoV in SARS-CoV-2 unexposed CVID individuals and compared it to healthy controls with and without exposure to SARS-CoV-2. The results showed that CVID patients less frequently had T-cells reactive to HCoV peptides, possibly due to regular IgG supplement therapy, which prevented HCoV common cold infections, but all CVID patients with HCoV reactive T-cells also possessed SARS-CoV-2 reactive T-cells. However, one of the study limitations was the inability to assess T-cell response in CVID patients post SARS-CoV-2 infection due to the fact that none of the CVID patients from that institution had COVID-19. Furthermore, a recent study by Gupta *et al.*[24] compared immune system responses to SARS-CoV-2 infection in a CVID patient and an immunocompetent control subject. The authors report that both patients failed to produce antiviral antibodies; however, they only developed mild to moderate clinical presentation with the

control subject having some residual symptoms while the CVID patient recovered completely. With these two reports, there is a premise that T-cells provide a significant protection against SARS-CoV-2 in CVID individuals. However, this observation remains to be determined.

Another concern are possible secondary infections among patients with COVID-19. A study by Lai *et al*.[25] established COVID-19 to be associated with simultaneous bacterial, viral and fungal infections. The prevalence of secondary infections varied, however, the authors declared that it could be up to 50% among non-survivors. In this review, co-pathogens were detected in body samples of four infected CVID patients (MRSA, β-lactamase producing *Escherichia coli*; *Aspergillus* spp., *Streptococcus agalactiae*; *Enterococcus faecium* and *Candida* spp., respectively), however, these findings may not directly imply infection as it can be colonization or contamination (Table 1). When comparing differences in treating critically ill COVID-19 patients, a notable finding by Huang *et al*.[26] was the increased use of invasive mechanical ventilation in Europe and USA in contrast to Asia. In this study, admission to ICU was required in 17 reported CVID patients, and out of the total number, 8 were from Europe, 8 from USA and 1 from Brazil.

Furthermore, as stated above, 89.1% of patients were on regular CVID treatment and 91.8% of them recovered from COVID-19. Also, this study detected five cases of no regularity in IG application where full recovery was still accomplished. Substitution of IGs is the only treatment option for CVID patients and studies have shown that the application of intravenous IG (IVIG) produces immunomodulatory and anti-inflammatory effect, particularly in high doses[12]. Several authors also assume that substitute IG products may possess antibodies capable of cross-reacting with SARS-CoV-2[12,27]. In their case report, Manian *et al*.[28] also point out that cross-reacting antibodies from supplemental IgG products may be non-neutralizing in nature and may produce false results in serologic testing for SARS-CoV-2. Nevertheless, there is a premise that IG replacement therapy contributes to CVID patient recovery and may also be useful in treating other patients with COVID-19[12,20,27,29]. During the COVID-19 pandemic, convalescent plasma infusion also emerged as a treatment option for CVID cases with severe COVID-19 manifestations. It provides two possible protective effects, i.e., the presence of neutralizing antibodies can inhibit virus from entering the cell and therefore restrict viral amplification, and it possesses an immunomodulatory effect[30]. The application of convalescent plasma in two reported cases demonstrated rapid improvement in patient clinical status and suggests its potential effectiveness in treating patients with humoral immunodeficiencies and COVID-19[31,32]. Furthermore, Pulvirenti *et al*.[33] evaluated quality of life in CVID patients during COVID-19 outbreak after being shifted to remote assistant program, that is, to home-based subcutaneous (SC) IG therapy. The authors concluded that this change had no impact on the patient quality of life.

The COVID-19 mortality rates show a strong age-related trend, especially in elderly persons with severe pre-existing comorbidities[4,34]. Results of this review showed that death percentage in CVID patients with SARS-CoV-2 infection was 11.6% and median age was 56.5 years. In comparison to the general population with COVID-19, patients with primary immunodeficiencies and COVID-19 have greater mortality[4,35-37]. Furthermore, a study by Shields *et al*.[36] pointed out that chronic lung disease was significantly associated with mortality in CVID patients.

Conclusion

In conclusion, CVID is a primary immune disorder with a limited number of reported cases after SARS-CoV-2 infection. CVID patients with COVID-19 usually present with fever, cough, dyspnea and fatigue while illness lasts for 19 days (median). Unexpectedly, CVID patients have high rates of recovery and it is still unknown to what degree primary immunodeficiency may have been a predisposing or protective factor against severe forms of COVID-19. Some findings also suggest that early application of IVIG or convalescent plasma infusion in CVID patients may positively influence the outcome of the disease. However, further investigations are necessary.

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Sažetak

OBIČNA VARIJABILNA IMUNODEFICIJENCIJA: ČIMBENIK KOJI POGODUJE ILI ŠTITI OD TEŠKIH KOMPLIKACIJA COVID-19?

Th. Ferenc i *T. Vilibić-Čavlek*

Koronavirusna bolest (COVID-19) novonastala je zarazna bolest koju uzrokuje SARS-CoV-2 (*severe acute respiratory syndrome coronavirus 2*). Uglavnom se očituje blagim simptomima nalik na običnu prehladu, ali može izazvati i teške, a katkada i smrtonosne komplikacije. Imunokompromitirani bolesnici poput onih s dijagnozom obične varijabilne imunodeficijencije (*common variable immunodeficiency*, CVID) također su dio zaražene populacije. Malo je objavljenih izvještaja o COVID-19 u bolesnika s CVID-om. Najčešće zabilježeni simptomi bili su vrućica, kašalj, dispneja i umor, dok je medijan trajanja bolesti iznosio 19 (interkvartilni raspon 14-26,5) dana. Ukupna stopa ozdravljenja iznosila je 88,4%. Još je uvijek nepoznanica djeluje li primarna imunodeficijencija kao predisponirajući ili zaštitni čimbenik protiv teških oblika COVID-19. Nadomjesna terapija imunoglobulinima (IG) jedina je opcija liječenja za bolesnike s CVID-om. Najnovija istraživanja ukazuju na to da bi u takvih bolesnika rana primjena intravenskih oblika IG ili konvalescentne plazme mogla povoljno utjecati na ishod bolesti COVID-19.

Ključne riječi: *Obična varijabilna imunodeficijencija; COVID-19; SARS-CoV-2*