Received: 21 November 2021 | Accepted: 19 January 2022

DOI: 10.1002/jmv.27614

SHORT COMMUNICATION

JOURNAL OF MEDICAL VIROLOGY WILEY

Immunological and virological aspects of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and hepatitis C virus

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Funding information

Fundação Oswaldo Cruz; Coordenação de Aperfeiçoamento de Pessoal de Nível Superior; Conselho Nacional de Desenvolvimento Científico e Tecnológico; Fundação Carlos Chagas Filho de Amparo à Pesquisa do Estado do Rio de Janeiro

Abstract

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection can generate a systemic inflammatory response, characterized by a cytokine storm and associated with an exaggerated release of proinflammatory cytokines, including tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and IL-17, all of which can affect the liver. Here, we aimed to evaluate the cytokine profiles of patients suffering from coronavirus disease (COVID)-19 and/or hepatitis. We subjected 87 patients to serology and/or polymerase chain reaction analysis for the hepatitis C virus. They were also tested for TNF-α, IL-6, and IL-17 using commercial immunoassay kits. The test results of the COVID-19/hepatitis C patients ($n = 8$) were compared with that of the negative controls ($n = 28$), hepatitis C patients ($n = 29$), and COVID-19 patients ($n = 22$). All COVID-19 patients (mono- and coinfected) expressed high levels of cytokines. The COVID-19/hepatitis patients exhibited higher levels of IL-6 (6.33 ± 3.9 pg/ml) and IL-17 (102.23 ± 2.7 pg/ml); however, TNF-α values were lower (68.08 ± 15.88 pg/ml), as compared with that of the hepatitis patients ($p < 0.001$), and lower than that of the COVID-19 patients and exceptionally for TNF-α ($p < 0.05$). These data highlight the importance of monitoring patients with hepatitis and COVID-19.

KEYWORDS

COVID-19, cytokines, hepatitis, IL-6, IL-17, TNF-α

1 | INTRODUCTION

Studies have shown that patients infected with severe acute respiratory syndrome coronavirus (SARS-CoV), Middle East respiratory syndrome coronavirus (MERS-CoV), and SARS-CoV-2 develop different degrees of liver damage,[1] including changes in the coagulation profile and increased levels of liver enzymes. However, the extent of liver damage has not yet been established, especially in patients with previous hepatic impairments, like liver injury due to viral hepatitis. Recent studies have demonstrated that liver damage occurs in approximately 60% of patients infected with SARS-CoV-2.[2] In fact, the proportion of liver damage is significantly higher in patients with severe COVID-19 than in the mild cases; moreover, in cases of death due to COVID-19, liver damage has been observed in 28%–30% of the patients.[3] Incidentally, the biochemistry profile report of COVID-19 patients published by the World Gastroenterology

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Organization (2021) mentions that an asymptomatic elevation of the liver enzymes, as detected in 14%–16% of the studied cases, is the most common observation. In fact, in >50% of the patients analyzed, there was an increase in alanine transferase (ALT) and aspartate aminotransferase (AST), along with a significant elevation of gamma-glutamyl transferase (GGT). Moreover, there was a slight elevation in the total bilirubin (BT) in 10% of the patients, while the alkaline phosphatase enzyme was typically in the normal range in mild cases of COVID-19. As compared with the severe COVID-19 cases, the liver enzymes were less elevated in the mild cases of the disease, only up to three times the value of the upper normal limit. In fact, among the studied patients, the serum AST levels were >40 IU/L in 52% of the patients who progressed to death and only in 16% of the ones who progressed satisfactorily. In general, changes in AST are more frequent, as compared with the changes in ALT in the severe patients.[4] Incidentally, hepatitis C virus (HCV) infection has a worldwide distribution, but the majority of the individuals infected with HCV remain asymptomatic, that is, they do not develop the acute form of the disease. Moreover, among the small percentage of acute hepatitis C cases, approximately 30% are cured spontaneously within 6 months, while the remaining 70% develop into the chronic form of the disease, which is associated with a high risk of liver cirrhosis and hepatocellular carcinoma.[5] Several theories have been proposed to explain the pathophysiology of SARS-CoV-2 and HCV coinfection. These include the intrinsic tropism of the virus for hepatocytes and bile ducts that may occur as a direct consequence of the complex humoral immune responses in these patients. Alternatively, it may be an indirect response to the cytokine storm, that is, the exaggerated production of proinflammatory cytokines during COVID-19. In fact, the latter theory is highly relevant, and it may be the key factor in the development and evolution of the clinical and laboratory disease profiles for SARS-CoV-2 and HCV coinfection.[6] Recent studies have reported a high production of proinflammatory cytokines in severe clinical cases of SARS-CoV-2 infection; additionally, the increased levels of IL-6, tumor necrosis factor-α (TNF-α), IL17A, IL-10, and interleukin-2 receptor (IL-2R) in patients diagnosed with chronic liver disease may associate the cytokine storm with the severity of COVID-19 in this group of patients.[7] In the present study, we evaluated the immunological profiles of COVID-19 patients, with and without liver changes, as well as patients suffering from only hepatitis C.

2 | MATERIALS AND METHODS

The enzymatic and immunological profiles of eight patients suffering from both acute COVID-19 and chronic hepatitis C were compared with the corresponding profiles of 28 healthy subjects (i.e., negative for both diseases), 22 patients with acute COVID-19, and 29 patients with chronic hepatitis C. The inclusion criteria for the study were: minimum age of 18 years, confirmed clinical and laboratory diagnosis (quantitative reverse transcription-polymerase chain reaction [RT-qPCR]) for COVID-19 and serology (anti-HCV reagent) and/or molecular diagnosis (HCV RNA detection) for hepatitis C, and signing the consent form. Blood and nasopharyngeal swab samples were collected to perform the necessary tests. The blood samples were used to determine the levels of ALT, AST, GGT, alkaline phosphatase, BT, indirect bilirubin (IB), and direct bilirubin (DB). Additionally, the complete blood count and platelet count were also evaluated. The ALT and AST levels were determined by UV-IFCC kinetics using Labmax Plenno equipment (Labtest, MG). Serum concentrations of GGT and alkaline phosphatase were determined using colorimetric methods (Labtest, MG). The concentrations of cytokines IL-6, IL-17, and TNF-α were evaluated using enzyme-linked immunosorbent assay (ELISA) kits (Peprotech TMB ELISA Development Kit), according to the manufacturer's instructions. All samples were stored in ultra-freezer at −80°C and the samples were defrosted and directly tested to cytokines.

The SARS-CoV-2 RNA was extracted from nasopharyngeal swab samples (by Qiagen commercial kit) and quantified using TaqMan RT-qPCR assay (AgPath-ID One-Step RT-PCR; Thermo Fisher Scientific). A set of different oligonucleotides and probes were used to detect the SARS-CoV-2 RNA.[8,9] Descriptive statistical analysis was performed by calculating the means and frequencies of the test results, and the possible relationships between categorical variables were evaluated using χ^2 or Fisher's exact test, whichever was applicable. Statistical significance was set at $p < 0.05$. Statistical analyses were performed using GraphPad Software Prism (version 9.0).

3 | RESULTS

We observed that the liver enzymes of the patients suffering from only hepatitis were higher than the normal reference values but lower than the expected thresholds for chronic HCV infection [AST: 79.12 (SD: 34.43); ALT: 48.08 (SD: 48.08), and GGT: 109.7 (SD: 109.7)][10] (Table 1). The cytokine values for these patients were: IL-6: 1.124 (SD: 0.07); IL-17: 82.45 (SD: 10.22); and TNF-α: 104.2 (SD: 6.18). Among the 87 enrolled individuals, 9.2% (8) were positive for hepatitis C as well as COVID-19 (confirmed by RT-qPCR), and out of them, 62.5% were females (5) and 37.5% (3) were males with a mean age of 55 ± 5 years. For the COVID-19/hepatitis C patient group, there was no significant increase in the AST [27.50 (SD: 10.07)] and ALT [37.38 (SD: 37.38)] values, as compared with the normal reference values. However, the mean value of GGT was high [103.3 (SD: 103.3)]. The mean cytokines values for these patients were: IL-6: 6.226 (SD: 4.00); IL-17: 102.4 (SD: 2.76); and TNF-α: 67.50 (SD: 17.79) (Table 1). Among the 87 enrolled individuals, 75.86% (22) tested positive for the SARS-CoV-2 RNA (detected by RT-qPCR), and they were classified into the COVID-19 group. In this group, 65.45% of the patients were men (12) and 45.45% were women (10), with an average age of 35 ± 15 years. Majority of them self-declared to be of white ethnicity (36.36%). Interestingly, the enzymatic profile of this group was within the normal reference range.

Incidentally, the mean values of the liver enzymes AST, ALT, and GGT were the highest in the group of patients mono-infected with

TABLE 1 Demographics and laboratory test results of study subjects (Rio de Janeiro, 2021)

	Control, *N* (%)	COVID-19, *N* (%)	COVID-19/Hepatitis, *N* (%)	Hepatitis, *N* (%)
Sample size	28 (32.18)	22 (25.29)	8 (9.2)	29 (33.33)
Gender				
Male	18 (64.29)	12 (54.55)	3 (37.5)	12 (41.38)
Female	10 (35.71)	10 (45.45)	5 (62.5)	16 (55.17)
Age (years)				
Mean	50 ± 4	35 ± 15	55 ± 5	50 ± 5
Skin color				
Black	11 (39.29)	2 (9.1)	0	6 (20.70)
Multiracial	3 (10.71)	6 (27.27)	4 (50)	2 (6.89)
White	14 (50)	8 (36.36)	4 (50)	6 (20.70)
Enzymes (UI/L)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
AST[a]	1.724 (2.52)	21.29 (9.98)	27.50 (10.07)	79.12 (34.43)[b]
ALT[a]	6.692 (8.98)	26.94 (20.43)	37.38 (37.38)	48.08 (48.08)[b]
GGT[a]	26.92 (20.26)	46.82 (50.23)	103.3 (103.3)	109.7 (109.7)[b]
Fibrosis-4 (FIB-4)				
<1.45		15	5	
<3.25 or >1.45			1	4
>3.25				10
No data	28	7	2	15
Cytokines (pg/ml)				
IL-6	1.724 (2.52)	16.37 (12.17)	6.226 (4.00)	1.124 (0.07)
IL-17	82.83 (11.51)	115.0 (11.08)	102.4 (2.76)	82.45 (10.22)
TNF-α	11.04 (7.90)	103.6 (50.02)	67.50 (17.79)	104.2 (6.18)
Nasal swab		CT (±SD)	CT (±SD)	
CT N1	ND	30.75 (6.39)	28.70 (7.68)	ND
CT N2	ND	30.68 (6.68)	29.72 (8.73)	ND
CT E	ND	33.39 (5.85)	ND	ND
Oropharyngeal swab		CT (±SD)	CT (±SD)	
CT N1	ND	29.13 (6.41)	26.67 (7.97)	ND
CT N2	ND	28.85 (6.90)	27.74 (9.47)	ND
CT E	ND	ND	ND	ND

Note: Nonparametric tests were used to analyze the differences among the mean values of IL-6, IL-17, TNF-α, AST, ALT, and GGT of the groups ($p < 0.05$).

Abbreviations: ALT, alanine transferase; AST, aspartate aminotransferase; C_t, cycle threshold; E, SARS-CoV-2 envelope genome; GGT, gamma-glutamyltransferase; IL-6, interleukin-6; IL-17, interleukin-17; *N*, sample; N1 and N2, nucleocapsid, ND, not detected; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SD, standard deviation; TNF-α, tumor necrosis factor-α.

[a]ALT reference value: 7–55 U/L, AST reference value: 8–48 U/L, and GGT reference value: 8–61 U/L.

[b]ALT reference value for chronic hepatitis: <31 U/L (female) and <41 U/L (male), AST reference value for chronic hepatitis: <31 U/L (female) and 37 U/L (male), and GGT reference value for chronic hepatitis: 8–61 U/L (male) and 5–36 U/L (female).

HCV. On the contrary, the liver enzymes of the COVID-19/HCV coinfected patients were within the normal reference values. Moreover, the SARS-CoV-2 mono-infected patients had lower levels of liver enzymes, as compared with that of the other two patient groups (Figure 1). With respect to the cytokine profiles, we did not record any increase in the mean values of IL-6 or IL-17 in the mono-infected HCV group, as compared with that of the control group. However, these patients expressed a higher mean value of TNF-α, as compared

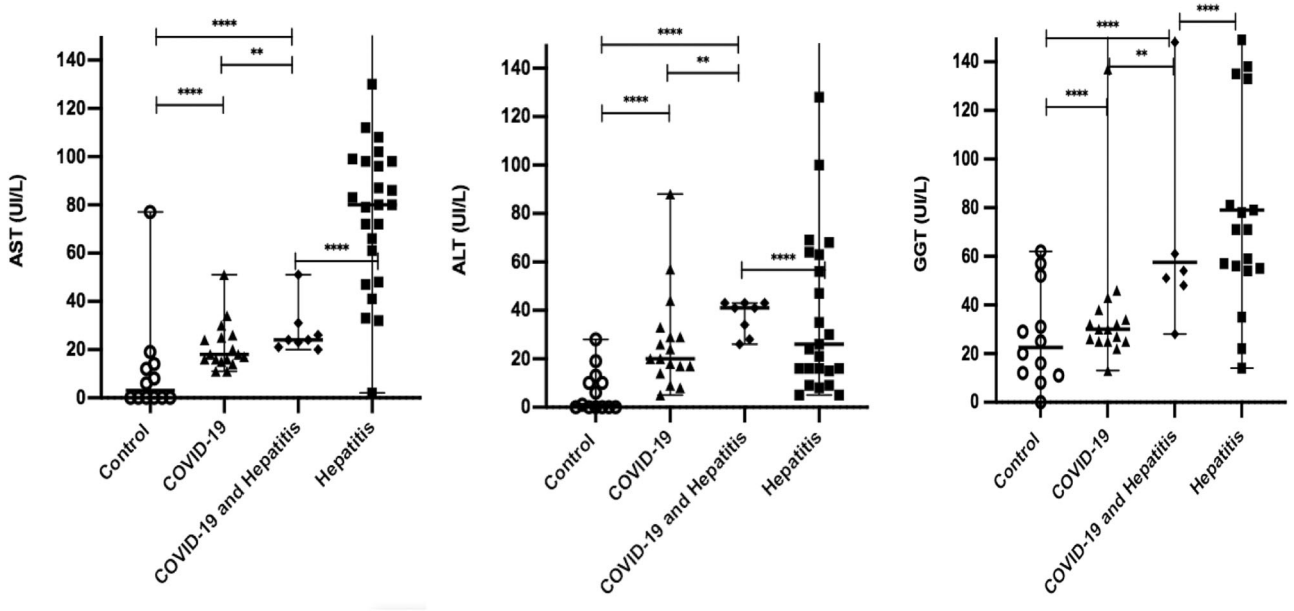

FIGURE 1 Aspartate aminotransferase (AST), alanine transferase (ALT), and gamma glutamyl transferase (GGT) profiles in control subjects, COVID-19 patients, and hepatitis patients with and without COVID-19. $^{**}p = 0.001$; $^{****}p < 0.0000$

with that of the control group (Figure 2). Incidentally, the COVID-19/hepatitis C patient group showed an increase in the cytokine levels, as compared with that of the control group. However, in comparison with the mono-infected HCV group, these patients showed an increase in IL-6 and IL-17, but not for TNF-α. On the contrary, the COVID-19 patient group showed increased values for both IL-6 and IL-17, but lower for TNF-α, as compared with the COVID-19/hepatitis C and only hepatitis C group where higher levels of TNF-α were observed. Hence, a significant increase ($p < 0.05$) in the serological levels of IL-6, IL-17 was observed in the COVID-19 and COVID-19/hepatitis C patient groups, and this differs for TNF-α levels as compared with mono-infected hepatitis and control groups (Figure 2).

4 | DISCUSSION

Despite the limited availability of data regarding the clinical and laboratory studies of COVID-19 and hepatitis C coinfection, some reports indicate a strong association between chronic HCV infection and a significant rise in the serum concentrations of liver enzymes AST, ALT, and GGT, which serve as inflammatory indicators of the liver and biliary tract.[6,11] Moreover, there is a possible relationship between the exaggerated systemic inflammatory response or cytokine storm that may occur during COVID-19 immune responses and the poor disease outcome in some groups of patients.[12] Indeed, some studies have revealed a noticeable elevation of proinflammatory cytokines, such as IL-2, IL-6, TNF-α, and so forth in the plasma of COVID-19 patients.[13,14] Similarly, in this study, we observed high cytokine levels in the COVID-19 patient group. Interestingly, in the COVID-19/hepatitis C patient group, the mean cytokine values were lower than that of the COVID-19 group, but the IL-6 and IL-17 were significantly higher than that of the hepatitis C group. Therefore, SARS-CoV-2 and HCV coinfection seem to modulate the cytokine immune response. Cycle threshold (C_t) values <40 were considered positive. In the COVID-19/hepatitis C group, we observed lower C_t values than those reported in previous studies, thereby suggesting a higher viral load. Recent studies reveal an association between high viral load and the severity of the disease.[15] In particular, in the SARS-CoV-2/HCV coinfected patients, a prolonged RNA shedding was observed,[16] thereby increasing their chances of developing severe immune suppression. Hence, in comparison with the non-HCV-infected patients, the ones with SARS-CoV-2/HCV coinfection had a higher viral load and a delayed recovery from the disease. This should be considered while determining the isolation period and care measures for the SARS-CoV-2-infected patients.

The FIB-4 index enabled the correct identification of patients with severe fibrosis (F3−F4) and cirrhosis. In this study, all HCV patients had chronic diseases and most of them, that have data available, had fibrosis >3.25, which means a positive predictive value to confirm the existence of significant fibrosis (F3−F4). Most of the patients with hepatitis and COVID-19 had Fibrosis Score <1.45. However, a recent study, that included 125 patients with chronic hepatitis C and COVID-19 coinfection, showed that patients with liver cirrhosis are susceptible to higher severity and mortality if infected with COVID-19.[17]

Studies of COVID-19 have shown a strong upregulation with and increased release of some proinflammatory cytokines such as IL-6, IL-17, TNF-α, IL-2, IL-10, and others. This has been associated with the hyperinflammatory phenomenon known as cytokine storm; in fact, one of the main features of the acute respiratory distress syndrome (ARDS) during the cytokine storm is a systemic dysregulated

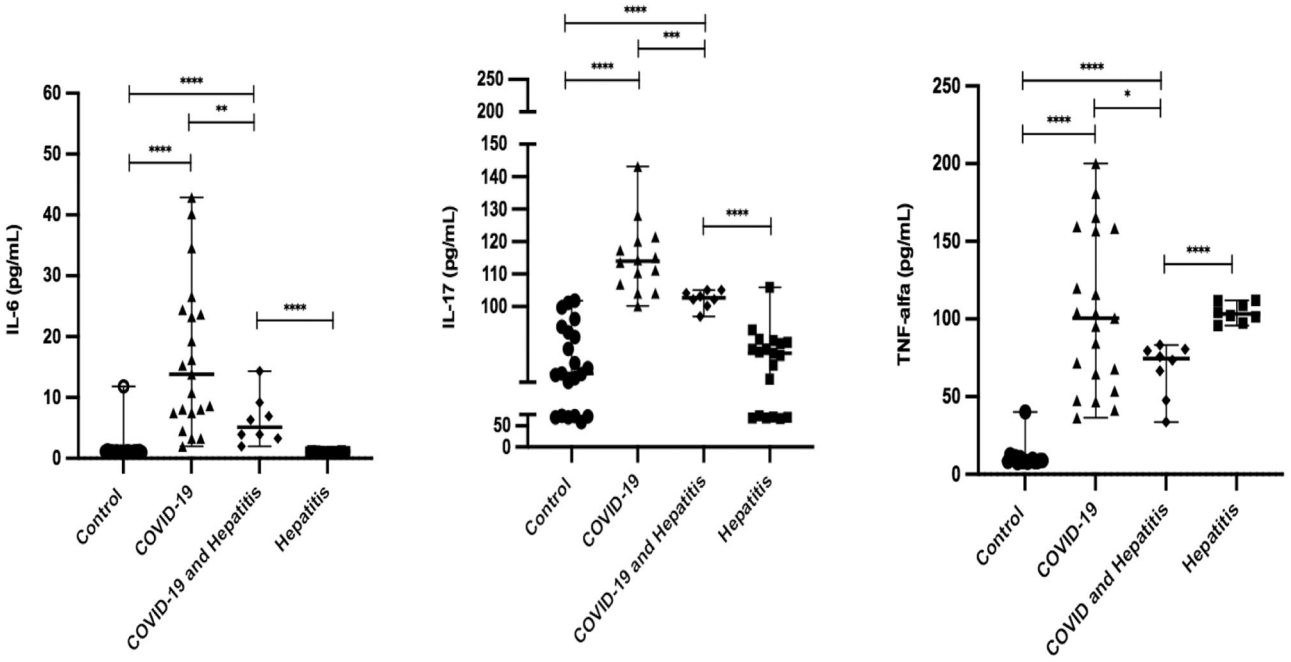

FIGURE 2 Interleukin-6 (IL-6), interleukin-17 (IL-17), and tumor necrosis factor α (TNF-α) in control subjects, COVID-19 patients, and hepatitis patients with and without COVID-19. *$p < 0.05$; **$p = 0.001$; ***$p < 0.0001$; ****$p < 0.0000$

inflammatory response as a result of the high expression of the aforementioned cytokines, which leads to aggravating the respiratory damages and multiorgan failure, including the liver.[18] Even though IL-6, IL-17, and TNF- α are not specific to SARS-CoV-2 nor of HCV or any other virus infection, studies in animals and clinical trials have demonstrated a significant increase in the production of cytokines, especially IL-6, IL-17A, IL-10, IL-2, TNF-α, and interferons in association with SARS-CoV-2 infection.[19] Some clinical studies have demonstrated a positive correlation with high levels of IL-17A in association with more severe forms of COVID-19, developing diffuse alveolar damage with an increase of neutrophils and proteins leading to edema in the alveolar space. The IL-17, which operates "upstream" of both IL-1 and IL-6 and results in a reduction of neutrophil recruitment, several factors known to play major roles in ARDS would be inhibited.[20] Furthermore, increased inflammatory cytokines (such as tumor necrosis factor-α [TNF-α] and interleukin-6 [IL-6]) are observed in COVID-19 patients, especially in the severe group.[21]

In conclusion, our observations demonstrate a significant increase in the serological levels of IL-6, IL-17 and interesting results of TNF-α in the SARS-CoV-2-infected patients; additionally, coinfection with HCV needs to be more investigated to further modulate the immune response. The results of this study are relevant since it is important to collect information about the co-occurrence of COVID-19 and hepatitis. Future studies should measure IL-10, IL-2, and IL-4 and use a larger sample size to understand the regulatory mechanisms of the systemic inflammation and liver injury involved in hepatitis patients with COVID-19. This will further help to elucidate the relevant aspects of the inflammatory process that is necessary for monitoring post-COVID infections in patients with previous liver disorders.

ACKNOWLEDGMENTS

This study was financed by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior—Brasil (CAPES; Finance Code 001), Fundação Carlos Chagas Filho de Amparo à Pesquisa do Estado do Rio de Janeiro (FAPERJ), INOVA Oswaldo Cruz Foundation and Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq).

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

ETHICS STATEMENT

This study was approved by Oswaldo Cruz Foundation ethical committee CAAE 30468620.5.0000.5248 approval number 4.112.243. All patients provided written informed consent.

AUTHOR CONTRIBUTIONS

Performed the experiments, analyses and interpretation of the data, draft of the article, final approval of the version to be published in accordance with all aspects of the work: Fabiola Justina Fumero León. *Sample collection, interviewing the patients, performed the experiments, data acquisition and final approval of the version to be published in accordance with all aspects of the work*: Lucas Lima da Silva, Alanna Calheiros Santos, Vanessa Duarte da Costa, Juliana Custódio Miguel, Julia Trece Marques, Giselle Prado Nascimento, Elisangela Ferreira da Silva. *Follow up the clinical status of the patients, final approval of the version to be published in accordance with all aspects of the work*:Lia Laura Lewis-Ximenez. *Wrote the project, study conception and design, analyses and interpretation of the data, draft of the article, critical revision of the article, final approval of the version to be published in*

accordance with all aspects of the work: Livia Melo Villar and Vanessa Salete de Paula.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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How to cite this article: León FJF, da Silva LL, Santos AC, et al. Immunological and virological aspects of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and hepatitis C virus. *J Med Virol*. 2022;94:2296-2301. doi:10.1002/jmv.27614