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**COVID-19 impact on the liver**

Baroiu L *et al*. COVID-19 and liver

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**Abstract**

The coronavirus disease 2019 (COVID-19) pandemic imposed arestructuring of global health systems by rethinking spaces used for the care of these patients and the additions of intensive care, infectious diseases and pneumology departments. This paper provides evidence on the presence of severe acute respiratory syndrome coronavirus 2 in hepatocytes and its direct cytopathic activity, as well as the degree of liver damage due to drug toxicity, inflammation and hypoxia in COVID-19. A review of clinical trials has quantified liver damage through both pathology and biochemistry studies. Additionally, we briefly present the results of a study conducted in our clinic on 849 patients admitted for COVID-19 treatment, of which 31 patients had pre-existing chronic liver disease and 388 patients had values above the normal limit for alanine aminotransferase, aspartate aminotransferase, and total bilirubin. It was observed that patients with abnormal liver tests were significantly statistically older, had more comorbidities and had a higher percentage of unfavourable evolution (death or transfer to intensive care). The conclusion of this paper is that the main causes of liver damage are direct viral aggression, coagulation dysfunction and endothelial damage, and patients with impaired liver function develop more severe forms of COVID-19 which requires special care by a multidisciplinary team that includes a hepatologist.

**Key Words:** COVID-19; Liver injury; Cytopathic effect; Hyper-inflammatory reaction; Drug toxicity; Biochemical changes

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**Core Tip:** The lung damage of these patients is primordial in the cascade of care that they receive, but also the liver damage induced by the direct action of the virus and the toxicity of the medication administered, has determined the active involvement of hepatologists in the care of these patients. The present paper aims to summarize the data published so far and personal experience, which may clarify the extent of liver damage in coronavirus disease 2019 and effective ways of therapeutic approach.

**INTRODUCTION**

On March 28, 2021, 127331692 cases and 2790624 deaths from coronavirus disease 2019 (COVID-19) were noted worldwide[1]. After a year of this pandemic, individuals think and work in a different way than they did a year ago. Adaptations to the new challenges of pathology were made rapidly by all medical specialties, including hepatologists who were included in multidisciplinary teams for the treatment of patients with COVID-19 and liver damage. Coronaviruses are large viruses, with sizes between 27 and 34 kilobases, and are enveloped single-stranded RNA viruses, from the family Coronaviridae and the subfamily Orthocoronavirinae. The epidemics of 2003 and 2012 were caused by the severe acute respiratory syndrome coronavirus (SARS-CoV) and the Middle East respiratory syndrome coronavirus (MERS-CoV). The new coronavirus (SARS-CoV-2), the etiological agent of the COVID-19 pandemic, seems to be a chimaeric variant of a coronavirus identified in bats in 2015 by Benvenuto *et al*[2] and has 82% genomic similarities to SARS-CoV and 50% genome sequence homology to MERS-CoV[3]. In 2003, in the SARS-CoV epidemic, approximately 60% of patients developed liver damage, and phylogenetic similarities suggested the possibility of the SARS-CoV-2 aggression on the liver[4].

**THE PATHOPHYSIOLOGICAL MECHANISMS OF HEPATIC AGGRESSION OF SARS-CoV-2**

The idea of ​​hepatic impairment in COVID-19 arose after the first evaluations of these patients, when alterations in liver function were observed and certified when the presence of SARS-CoV-2 in liver tissue was confirmed[5].

Liver damage in COVID-19 has been attributed to the direct attack by SARS-CoV-2, drug toxicity in COVID-19 therapy, acute inflammatory damage and hypoxia caused by pneumonia.

Direct attack by SARS-CoV-2 on the liver includes the direct cytopathic effect on hepatocytes and cholangiocytes, and the effects of coagulopathy and endothelial aggression in small intrahepatic vessels.

The mechanisms of direct hepatic destruction, in COVID-19, include its presence on the surface of endothelial cells in small blood vessels (endothelial layer of small blood vessels), and hepatocytes (2.6%), but especially on the surface of bile duct cells (cholangiocytes) (59.7%) of angiotensin 2 converting enzyme (ACE2) receptors, which are considered the cellular receptor for SARS-CoV-2. The expression level of these cholangiocyte receptors is also similar to that of lung type 2 alveolar cells, suggesting that the liver may be a potential target for SARS-CoV-2[6].

Another receptor, transmembrane protease serine 2 (TMPRSS2), which interacts with SARS-CoV-2, what is present on cholangiocytes and hepatocytes, is important for proteolytic activation and also for spread of virus particles[7].

Ultrastructural analysis of post-mortem liver biopsies from patients who died of COVID-19 observed coronavirus particles in the cytoplasm of hepatocytes[8]. Hepatocyte lesions included cell membrane dysfunction, mitochondrial swelling, and dilated endoplasmic reticulum. These observations documented the ability of the virus to replicate in hepatocytes and demonstrated the link between cytopathic damage to hepatocytes and impaired liver function[8].

Another mechanism involved in liver injury is the extensive vascular damage to the hepatic portal system in the acute form (thrombosis and luminal ectasia) or chronic changes (fibrous thickening of the vascular wall), identified post-mortem in patients with COVID-19. These observations suggest that endothelial damage and coagulation dysfunction may be the major trigger in the pathogenesis of COVID-19 liver lesions[9].

The hyper-inflammatory reaction of COVID-19 may cause liver damage. In the evolution of COVID-19, a massive release of pro-inflammatory cytokines was observed, with increasing interleukin (IL)-6, lactate dehydrogenase, C-reactive protein, and ferritin concentrations.

This cytokine storm syndrome is accompanied by organ dysfunction, including progressive liver damage and liver failure[10-13]. IL-6 is a potent cytokine involved in inflammation and liver regeneration[14]. IL-6 production occurs in immune cells[14], fibroblasts, endothelial cells[15] and hepatocytes[13,16]. In correlation with the pathophysiology of the implication of systemic inflammation and specifically IL-6 on liver damage, clinical studies have observed that the growth of IL-6, in patients with COVID-19 with increased aspartate aminotransferase (AST), serves as a fuel for liver injury, which is more pronounced in patients with COVID-19, with a more severe inflammatory response (sometimes requiring intensive care measures)[17]. The concomitant increases in IL-6, ferritine, and alanine aminotransferase (ALT) levels, and also the decreases in platelet count and albumin concentration, show significant hepatic lesions during COVID-19[18]. Another study suggested collateral liver damage caused by SARS-CoV-2, induced by cytotoxic T cells 2[19].

Hypoxia caused by respiratory failure in COVID-19 affects hepatocyte metabolism and may cause liver damage. A study reported the association of liver enzyme abnormalities with higher radiological scores, disease severity, higher alveolar-arterial oxygen partial pressure difference, higher ferritin, higher gamma-glutamyl transferase, lower albumin, and decreased lymphocytes B and CD4+ T cells[8]. Other clinical studies have observed the predictive nature of aggressive lung damage, observed on computer pulmonary tomography, for liver damage and the need for careful monitoring of liver function in these patients.

Post-drug hepatotoxicity in COVID-19 was argued by the occurrence of hepatic cytolysis during hospitalization and its association with allergic eruptions in convalescence. Pathological studies have detected moderate microvesicular steatosis with mild liver inflammation that can be attributed to drug hepatotoxicity[20].

The drugs used in the treatment of COVID-19 with hepatotoxic potential are as follows: (1) Remdesivir is a nucleotide analogue, which was developed for the treatment of chronic hepatitis C, and later tested for Ebola virus but without clinical efficacy, now in the COVID-19 treatment guidelines. The manufacturer indicates very common side effects in the leaflet (these may affect more than 1 in 10 patients), such as elevated liver enzymes without recommending dose adjustments for liver or kidney failure. Remdesivir therapy was not performed in patients with AST and ALT greater than 5 times the normal amount. A study of 53 patients observed increased liver enzymes, in 23% of patients, and remdesivir was discontinued in 2 patients[21]. Another multicentre study observed that aminotransferases increased by 5% and serum bilirubin increased by 10% in the remdesivir-treated group[22]; (2) Favipravir is a guanine analogue approved in Japan for the treatment of influenza, in which the manufacturer notes only teratogenic side effects and has been shown to be well tolerated by the liver in the treatment of patients with COVID-19. Clinical studies on favipiravir therapy noted elevated liver enzymes between 2.6% and 7.6% of patients with COVID-19[23,24]. (3) Lopinavir-ritonavir, a protease inhibitor-used for treatment of HIV has reported hepatotoxicity of 2%-10% in the Cao study in patients with severe forms of COVID-19 and increased the rate of liver damage 4 times in the Cai study[25,26]. The ELACOI trial, observed 4.8% of patients with a 2.5 fold elevation in liver enzymes[27]; (4) Antipyretics, especially paracetamol, have hepatotoxic potential, and the dose should not exceed 2-3 g/d, which is considered a safe dose in patients with chronic liver disease[28]; (5) Dexamethasone, with its anti-fibrotic and anti-inflammatory properties, is one of the most studied immunomodulators in SARS-CoV-2 therapy[29], with possible benefits in patients with COVID-19 and acute liver failure; (6) Tocilizumab is a anti IL-6 receptors, humanized monoclonal antibody that is being used in severe forms of COVID-19 for cytokine release syndrome[10]. Liver enzyme elevation occurs frequently after tocilizumab treatment, with rare descriptions of severe liver injury[30]. Tocilizumab increases the risk of reactivation of hepatitis B virus[31]; (7) Hydroxychloroquine is a possible treatment, with a low incidence of drug-induced liver failure but it may concentrate in the liver and should be used with caution in patients with chronic liver disease[32]; and (8) Azithromycin may cause idiosyncratic drug-induced liver failure, which is manifested by cholestatic hepatitis 1-3 wk after initiation of treatment. Hepatocellular necrosis is rare and begins a few days after starting treatment. A hepatocellular pattern is predominant, and most patients recover completely[33].

The recommendations regarding the diagnosis of drug-induced liver failure, included clinical and paraclinical criteria. Paraclinical criteria are an increase in ALT greater than 5 times the normal value or an increase in alkaline phosphatase greater than 2 times the normal value, in the absence of a known bone pathology or an ALT increase greater than 3 times the normal value with a simultaneous increase in total bilirubin (TBIL) greater than 2 times the normal value. Clinical criteria are the presence of classic symptoms of hepatic injury: jaundice, encephalopathy, haemorrhage (secondary to coagulopathy), ascites or non-specific symptoms, such as fatigue, anorexia, nausea, vomiting, fever, abdominal pain, itching, and rash[34].

The principles of drug-induced liver failure treatment are based on discontinuation of hepatotoxicity. This principle is difficult to follow in patients with severe COVID-19, and the decision to change treatment must be made by a multidisciplinary team of infectious diseases, intensive care and gastroenterology physicians respecting the risk-benefit principle[35,36].

**COVID-19 LIVER PATHOLOGICAL ANATOMY**

The first post-mortem liver biopsies were performed by Xu *et al*[20]. They observed a moderate rank of microvesicular steatosis and mild lobular and portal activity. Liver damage may appear as an effect of the direct cytopathic action of SARS-CoV-2 or drug toxicity. Another study found thrombosis, luminal ectasia and fibrous thickening of the vascular wall, suggesting that endothelial damage and coagulation dysfunction are involved in pathogenesis of hepatic impairment in COVID-19[9].

Wang *et al*[8]'s study observed mainly moderate microvesicular and mild macrovesicular steatosis, and focal lobular inflammation with lymphocytes infiltration. Portal tracts inflammation with lymphocytic infiltrate was rare. Lesions suggestive of hepatic ischemia (centrilobular necrosis), septic aggression (centrilobular necrosis, canalicular/ductular cholestasis, or non-bacterial cholangitis), or post-drug toxicity (eosinophiles infiltration, fibrin deposition, cholestasis, granuloma, interface hepatitis, massive central necrosis) have not been observed, suggesting that these mechanisms are not significantly involved in liver injury.

The Cai *et al*[24]'s study highlighted the presence of SARS-CoV-2 viral particles in the cytoplasm of hepatocytes, demonstrating the possibility of the virus entering the hepatocyte, as well as its replication in the hepatocyte. The changes described in hepatocytes were: swelling of the mitochondria and, dilation of both the endoplasmic reticulum and affected cell membrane, demonstrating the cytopathic effect of SARS-CoV-2 in hepatocytes. Ki67 immunohistochemistry has shown that the main histological changes in the liver of patients with COVID-19 are the presence of massive apoptosis and syncytial and multinucleated hepatocytes. CD4 and CD8 cells are rare in liver tissue which emphasizes that the direct viral cytopathic effect is the main factor of aggression and not immune conflict.

**BIOCHEMICAL CHANGES IN COVID-19 HEPATIC INJURY**

Liver damage in COVID-19 is common in clinical practice (Table 1). The change in AST/ALT levels can be attributed to hepatocyte, myocardial and muscular lesions. Most patients​​ (60%) with abnormal AST/ALT values ​​show a slight increase between 1-2 normal values; approximately 30% of patients had moderate liver injury (between 2 and 5 times higher than the normal value); and less than 10% of patients had severe liver injury (ALT more than 5 times higher than the normal value)[37,38]. But, much higher values​​, such as ALT = 7590 U/L and AST = 1445 U/L, were also reported in a patient with a severe form of COVID-19[39].

The increase in ALT, AST in children is usually below twice the normal value, severe liver damage being very rare in children[40,41].

The TBIL is, in most cases of COVID-19, normal or modestly elevated[37,42-44]. Elevated gamma glutamyl transferase was observed in 6% of COVID-19 patients and elevated alkaline phosphatase was observed in 21% of COVID-19 patients[45]. Elevated alkaline phosphatase was associated with an increased risk of death of COVID-19[46].

Low serum albumin was considered a marker of severe evolution of COVID-19[37,47-50].

Studies also found correlations between the degree of liver damage and severity of COVID-19, as well as the negative prognosis of patients with COVID-19 and liver injury[45,51].

In our clinic, the Second Infectious Diseases Clinic of the Infectious Diseases Clinical Hospital “Sf. Cuv. Parascheva”, Galati, Romania, we conducted a retrospective study of 849 patients hospitalized with COVID-19 between January 3, 2020 and November 30, 2020. Of these, 31 patients (3.65%) had a history of chronic liver disease, and 388 patients (45.70%) presented at biochemical evaluation with either ALT or AST or TBIL above normal values. The characteristics of the group with pre-existing chronic liver injury and of the group with acute liver injury were compared with the characteristics of the total group of patients with COVID-19 and are presented in Table 2. Statistical analysis was performed with MedCalc version 19.6.4.[52].

The group of 31 patients with pre-existing chronic liver disease included one patient with toxic liver cirrhosis, 11 patients with chronic hepatitis B, 2 patients with chronic hepatitis B and D, 6 patients with chronic hepatitis C, 6 patients with chronic toxic hepatitis and 5 patients with hepatic steatosis.

An increase in ALT between 1 and 3 times the normal value was observed in 261 patients (30.74%) and, between 3 and 5 times the normal value in 65 patients (7.65%). An increase in AST between 1 and 3 times the normal value was observed in 299 patients (35.21%) and, between 3 and 5 times the normal value in 35 patients (4.12%). Lastly, an increase in TBIL above the normal value was observed in 27 patients (3.18%).

The study conducted in our clinic observed the appearance of COVID-19 with the need for hospitalization in patients with an average age of 50.21 years, and patients with liver damage were significantly older (average age 53.04 years).

Cumulation of comorbidities, quantified by the Charlson score, was significantly higher in the group with pre-existing liver diseases and in the group with COVID-19-induced liver injury. Patients with abnormal liver function had a, statistically significant, higher percentage of unfavourable evolutions (death or transfer of intensive care) compared to patients in the total group with COVID-19.

**THE IMPACT OF COVID-19 ON LIVER WITH PRE-EXISTING CHRONIC INJURY**

Nonalcoholic fatty liver disease (NAFLD) is affecting a quarter of the world's population[53] and is reported in 2-11% of patients with chronic liver disease who have had COVID-19[3].

Patients with obesity, diabetes mellitus and hypertension are frequently associated with NAFLD and are the recognized category of patients at risk of severe evolution of COVID-19[54].

NAFLD is noted in clinical trials as an independent risk factor for increased TGP in patients with COVID-19[19,55,56] and it is accompanied by a longer period of viral clearance compared to patients without NAFLD (17.5 ± 5.2 d *vs* 12.1 ± 4.4 d, *P* < 0.0001)[19].

The association of NAFLD in the comorbidity palette of the patient with COVID-19 is considered by some clinical studies as an unfavorable prognostic factor[19,38,57] and by other clinical studies without influence on the prognosis of COVID-19[55,56] which argues the need to conduct studies on larger batches of COVID-19 patients for clear conclusions.

Chronic viral hepatitis was shown to be a negative prognostic factor in patients with COVID-19. A meta-analysis of 257 patients with COVID-19 of which 235 with chronic hepatitis B and 22 patients with chronic hepatitis C scoring a 6% death rate in those with HBV and 13 % in those with HCV, the transfer rate in the ICU 14.1% in HBV and 21.4% in HCV, significantly increased compared to patients without chronic viral hepatitis[58,59].

Few clinical trials have examined the risk of reactivation of hepatitis B in patients with severe forms of COVID-19 requiring immunosuppressive therapy[60,61]. The conclusion of these studies and the AASLD guideline is to consider prophylactic antiviral therapy in these patients[38,61].

Patients with autoimmune hepatitis were not associated with an increased risk of severe progression or death from COVID-19[62].

Alcohol-associated liver diseases, cirrhosis and hepatocellular carcinoma are associated with high mortality rates through COVID-19[50,63-66].

Chronic liver disease as a whole is associated with an increased risk of mortality from COVID-19 (risk ratio 2.8 in a cohort of 2780 patients) but cirrhosis appears to have the highest risk of mortality (risk ratio 4.6)[63].

The recommendations of the AASLD guide are for the continuation of liver transplants, respecting all the rules for minimizing the transmission of SARS-CoV-2 and the local protocols of each transplant clinic that optimizes the existence of the resources necessary for performing the liver transplant[38].

**CONCLUSION**

Phylogenetic similarities with SARS-CoV and MERS-CoV suggest that SARS-CoV-2 may cause liver damage. The identification of ACE2 receptors on the surface of hepatocytes and cholangiocytes has opened research on the direct aggression of SARS-CoV-2 on the liver. The detection of viral particles in hepatocytes certified the direct aggression of the virus on the liver. The study of post-mortem liver biopsies suggested that endothelial damage and coagulation dysfunction are the leading cause of liver injury in COVID-19. Elevated levels of acute phase proteins, especially IL-6, correlate with elevated transaminases and severe forms of COVID-19 in clinical trials. Hypoxia caused by respiratory failure in COVID-19 affects hepatocyte metabolism, and clinical trials have noted correlations between massive pulmonary destruction, quantified by computer pulmonary tomography, and acute liver failure. Antivirals, antibiotics, antipyretics, and immunomodulators used in COVID-19 therapy may cause hepatotoxicity, but to a small extent, and should be discontinued and replaced if drug-induced acute liver failure is suspected. Moderate ALT and AST changes in COVID-19 are common in clinical practice. Significant changes in AST and ALT are predictive of unfavourable evolution of COVID-19. Our study observed that patients with elevated ALT, AST, and TBIL were significantly older, had more comorbidities and more unfavourable evolution than the total group of patients with COVID-19. Chronic liver diseases are associated with an increased risk of mortality from COVID-19, especially cirrhosis and hepatic adenocarcinoma.

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**Footnotes**

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**Table 1 Biochemical changes in patients with coronavirus disease 2019 and pre-existing chronic liver diseases in clinical trials**

|  |  |  |  |
| --- | --- | --- | --- |
| **Ref.** | **Patients with COVID-19** | **Patients with abnormal liver function (%)** | **Patients with pre-existing liver diseases (%)** |
| Guan *et al*[67] | 1,099 | 21.3 abnormal ALT; 22.2 abnormal AST | 2.3 |
| Huang *et al*[68] | 41 | 31 | 2 |
| Chen *et al*[39] | 99 | 43 | NA |
| Wang *et al*[69] | 138 | NA | 2.9 |
| Shi *et al*[70] | 81 | 53.1 | 8.6 |
| Xu *et al*[71] | 62 | 16.1 | 11 |
| Yang *et al*[72] | 52 | 29 | NA |
| Zhang *et al*[3] | 56 | 28.6 | 3.6 |
| Cai *et al*[25] | 298 | 14.8 abnormal ALT; 8.7 abnormal AST | 2.7 |
| Cao *et al*[26] | 128 | 43.8 abnormal ALT; 44.1 abnormal AST | NA |
| Zhang *et al*[73] | 82 | 30.6 abnormal ALT; 61.1 abnormal AST; 30.6 abnormal TBIL | 2.4 |
| Fan *et al*[74] | 148 | 21.6 abnormal AST; 18.2 abnormal ALT; 17.6 abnormal GGT; 6.1 abnormal TBIL | NA |
| Huang *et al*[75] | 36 | 13.3 abnormal ALT; 58.1 abnormal AST; 12.9 abnormal TBIL | NA |
| Li *et al*[76] | 85 | 24.7 abnormal ALT | 7.05 |
| Xie *et al*[77] | 79 | 31.6 abnormal ALT; 35.4 abnormal AST; 5.1 abnormal TBIL | 0 |
| Zhang *et al*[78] | 115 | 9.57 abnormal ALT; 4.78 abnormal AST | 0 |
| Zhao *et al*[79] | 19 | 27.78 abnormal ALT; 44.4 abnormal AST; GGT | 5.26 |
| Sultan *et al*[32] | Meta-analysis of 47 studies 10,890 patients | 15.0 abnormal AST; 15.0 abnormal ALT; 16.7 abnormal TBIL | NA |
| Effenber *et al*[17] | 96 | 42 abnormal AST | NA |
| Mantovani *et al*[80] | Meta-analysis of11 studies 2,034 patients | NA | 3 |
| Hundt *et al*[81] | 1,827 | Abnormal at admission (AST 66.9, ALT 41.6, ALP 13.5, and TBIL 4.3) and peak hospitalization (AST 83.4, ALT 61.6, ALP 22.7, and TBIL 16.1) | NA |
| Cai *et al*[24] | 417 | 76.3 abnormal ALT, AST, TBIL and GGT | NA |
| Wang *et al*[8] | 156 | 41.0 abnormal ALT and, AST | NA |
| Velarde-Ruiz Velasco *et al*[82] | 99 | 35 abnormal AST; 28 abnormal ALT; 98 abnormal albumin | NA |
| Our unpublished data | 849 | 38.39 abnormal ALT39.33 abnormal AST3.18 abnormal TBIL | 3.65 |

COVID-19: Coronavirus disease 2019; ALT: alanine aminotransferase; AST: aspartate aminotransferase; GGT: gamma-glutamyl transferase; TBIL: Total bilirubin; NA: Not available.

**Table 2 Demographic and clinical characteristics**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Total COVID-19 patients** | **Patients with abnormal liver function** | **Patients with pre-existing liver disease** |
| Age (yr) |  |  |  |
| Minimum-maximum | 0.083-97 | 0.33-97 | 32-88 |
| Average | 50.21 | 53.04 (*P* = 0.0215) | 55.70 (*P* = 0.1351) |
| 95%CI | 48.85-51.58 | 51.09-54.99 | 51.08-60.33 |
| Female (%) | 54.18 | 52.31 (*P* = 0.5820) | 48.38 (*P* = 0.6506) |
| Charlson score (%patients) |  |  |  |
| 0 | 41.08 | 34.02 (*P* = 0.0190) | 16.12 (*P* = 0.0094) |
| 1-2 | 32.58 | 34.79 (*P* = 0.4664) | 41.93 (*P* = 0.3592) |
| 3-4 | 16.29 | 18.55 (*P* = 0.3585) | 29.03 (*P* = 0.1049) |
| 5-11 | 10.03 | 12.62 (*P* = 0.2034) | 12.90 (*P* = 0.8281) |
| Number of days of hospitalization |  |  |  |
| Minimum-maximum | 1-80 | 1-52 | 1-35 |
| Average | 11.06 | 11.53 (*P* = 0.3034) | 11.35 (*P* = 0.8097) |
| 95%CI | 10.55-11.58 | 10.83-12.24 | 9.12-13.58 |
| Curb 65 score (%) |  |  |  |
| 0 | 12.43 | 10.34 (*P* = 0.3355) | 10.00 (*P* = 0.8997) |
| 1 | 62.18 | 59.41 (*P* = 0.3869) | 63.33 (*P* = 0.9531) |
| 2 | 23.11 | 26.52 (*P* = 0.2194) | 23.33 (*P* = 0.8506) |
| 3 | 3.51 | 3.71 (*P* = 0.9914) | 3.33 (*P* = 0.6573) |
| Unfavourable evolution (death or transfer to intensive care) (%) | 4.71 | 7.73 (*P* = 0.0454) | 12.90 (*P* = 0.1126) |

COVID-19: Coronavirus disease 2019; CI: Confidence interval.