Journal of Surgery
Leite AA, et al. J Surg 10: 11251
www.doi.org/10.29011/2575-9760.11251
www.gavinpublishers.com
Research Article

Hepatobiliary Ultrasound Findings and Outcomes in Severe Covid-19

Alice Abath Leite[1-3*], Camila Silva Bezerra[1-3], Thaís Ramos da Costa[1,2,4,5], Felipe Alves Mourato[1,5], Esdras Marques Lins[1-3], Emmanuelle Tenório Albuquerque Madruga Godoi[1,6], Lúcia Helena de Oliveira Cordeiro[4,6], Maria Cristina Falcão Raposo[7], Simone Cristina Soares Brandão[1,6,8]

[1]Post-Graduation Program in Surgery, Universidade Federal de Pernambuco (UFPE), Recife, PE, Brazil

[2]Instituto de Medicina Integral Professor Fernando Figueira (IMIP), Recife, PE, Brazil

[3]Faculdade Pernambucana de Saúde, Recife, PE, Brazil

[4]Hospital Barão de Lucena, Recife, PE, Brazil

[5]Empresa brasileira de serviços hospitalares EBSERH - Hospital das Clínicas da Universidade Federal de Pernambuco (HC-UFPE), Recife, PE, Brazil

[6]Department of Internal Medicine, Universidade Federal de Pernambuco (UFPE), Recife, PE, Brazil

[7]Department of Statistics, Universidade Federal de Pernambuco (UFPE), Recife, PE, Brazil

[8]Department of Diagnostic Imaging, Hospital das Clínicas da Universidade Federal de Pernambuco (HC-UFPE), Recife, PE, Brazil

[*]**Corresponding author:** Alice Abath Leite, Post-GraduationProgram in Surgery - Universidade Federal de Pernambuco (PPGC-UFPE), Hospital das Clínicas - Campus UFPE, Av. Prof. Moraes Rego,"s/nº - Bloco "A" - Cidade Universitária, Recife, PE, Brazil

Citation: Leite AA, Bezerra CS, da Costa TR, Mourato FA, Lins EM, et al. (2025) Hepatobiliary Ultrasound Findings and Outcomes in Severe Covid-19. J Surg 10: 11251 DOI: 10.29011/2575-9760.011251

Received Date: 02 February 2025; **Accepted Date:** 07 February 2025; **Published Date:** 10 February 2025

Abstract

Background: COVID-19 is an infectious multisystem disease caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). Although abdominal manifestations have been observed in these patients, the relationship between hepatobiliary abnormalities and the progression of COVID-19 remains poorly defined. Imaging exams - such as Computed Tomography (CT) and magnetic resonance imaging (MRI) - have revealed hepatic and bile duct changes in these patients. However, few studies have demonstrated these findings through Ultrasound (US).

Objective: To determine if abdominal US can be used as a prognostic marker in severe COVID-19 patients.

Methods: A prospective, observational study in three specialized COVID-19 hospitals in Brazil from July 2020 to February 2021. We evaluated a convenience sample of inpatients, in both the intensive care unit (ICU) and nursery. Hepatobiliary US was performed by three radiologists who were blinded to all other patient-associated laboratory and clinical data. Information on sociodemographic and clinical variables was obtained from physical and electronic medical records. Fisher's exact test or chi-square test was performed according to data characteristics for each categorical variable.

Results: 59 patients (with a mean age of 60 ± 15 years) were included in the study; of these, 36 (61%) were male and 48 (81%) were admitted to the Intensive Care Unit (ICU). Of them, 28 (47%) succumbed. Changes in gallbladder wall or bile content (excluding the presence of gallstones), were correlated with death.

Conclusion: COVID-19 patients with cholestasis and gallbladder wall-thickening had higher mortality, and these ultrasonographic findings can be used as a prognostic factor.

Keywords: COVID-19; Gallbladder; Liver; SARS-CoV-2; Ultrasonography

Introduction

COVID-19 is an infectious multisystem disease caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). [1] Its severe form can affect multiple organs, and endotheliitis is a pathophysiological explanation for the impairment of tissue perfusion and organ failure. Although abdominal manifestations have been observed in these patients, the relationship between hepatobiliary abnormalities and the progression of COVID-19 remains poorly defined. [2-7] Liver damage in COVID-19 appears to be multifactorial: it may arise from increased expression of angiotensin-converting enzyme 2 (ACE2) in liver cells (like the expression in lung cells), direct viral infection, immune response, endothelial dysfunction, and even drug therapy. [8-18] Elevated levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), and gamma-glutamyltransferase (GGT) are frequently observed in patients with COVID-19.[19-22] Previous investigations have shown that up to 53% of patients exhibit altered AST and ALT levels, and approximately 50% may develop increased GGT levels. Increased serum bilirubin levels have also been reported. [4,19-21] Imaging examinations such as Computed Tomography (CT) or magnetic resonance imaging (MRI) in hospitalized patients with COVID-19 have revealed hepatic and bile duct changes, including hepatic parenchymal heterogeneity, periportal edema, and cholestasis. [5-7,19,23-26] Few studies have demonstrated these findings through Ultrasound (US) and correlated them with clinical variables, although US is a widely available, noninvasive tool for investigating hepatobiliary abnormalities. [6,27] There are several advantages to incorporating US evaluation in patients with severe COVID-19, such as the integration of sonographic findings with the patient's medical history and clinical examination, especially in acutely unwell adult patients, those in the Intensive Care Unit (ICU), and patients confined to bed. [8,27] Therefore, monitoring liver function is essential for properly managing these patients and formulating targeted therapies, including creating and implementing liver protection protocols. In this context, Ultrasound (US) could be highly valuable for liver monitoring, as it is already established as an accessible, low-cost imaging method useful for evaluating both acute and chronic liver and biliary abnormalities. [8,28] In this context, the objective of this study is to determine if abdominal US can be used as a prognostic marker in severe COVID-19 patients.

Material and Methods

Patients and Study Design

We conducted a prospective, observational study in three specialized COVID-19 hospitals in Brazil from July 2020 to February 2021. We evaluated a convenience sample of inpatients, in both the intensive care unit (ICU) and nursery, all of whom were aged 18 years or older and had confirmed SARS-CoV-2 infection as determined by reverse transcription polymerase chain reaction (RT-PCR). Severe COVID-19 was defined as meeting at least one of the following criteria: respiratory distress with a respiration rate exceeding 30 breaths per minute, resting fingertip blood oxygen saturation below 93%, the need for mechanical ventilation, shock, or multiple organ failure. We excluded patients younger than 18 years and those who refused to participate or had incomplete medical records.

Ultrasound Protocol and Data Collection

Ultrasounds were performed at the bedside using LOGIQ systems (GE Healthcare, Waukesha, WI, USA) equipped with 12L-RS (12MHz) linear and 4C-RS (4MHz) convex transducers. These examinations were performed by three radiologists (with 4-10 years of experience), who were aware of the RT-PCR results for SARS-CoV-2 but were blinded to all other patient-associated laboratory and clinical data.

The US protocol for hepatobiliary study included evaluation of the liver, intrahepatic bile ducts, extrahepatic bile ducts, and

gallbladder, searching for the following changes: signs of liver disease by fat deposit, signs of chronic liver disease, periportal thickening, hepatomegaly, evidence of cholestasis, gallbladder wall-thickening, presence of gallstones, and ascites. Criteria were specified during the US and during the image review aiming to reduce false-positive observations and those prone to subjectivity: (a) hepatic steatosis was defined as increased parenchymal echogenicity obscuring periportal planes and with attenuation of the posterior acoustic beam; (b) the assessment of chronic liver disease via ultrasound involved the evaluation of several factors, including liver size, the texture of the liver, bluntness of the liver edge, and the presence of nodularity on the hepatic surface; (c) hepatomegaly was considered when the liver length was greater than 15.5 cm, except cases favorable to the Riedel's lobe anatomical variant; (d) gallbladder distention was defined when transverse dimension > 4 cm; (e) cholestasis when echogenic debris was accumulated inside the gallbladder without a posterior acoustic shadow; and (f) parietal gallbladder thickening when thickness > 3 mm in a properly distended gallbladder [6]. The sonographic data were saved on electronic devices and analyzed in a clinical-radiological setting by the research team. For inclusion in the study, at least two of the three researchers had to observe and agree upon the findings independently. Any discrepancies in the initial interpretation of the data were resolved by consensus among the researchers.

Following the analysis of imaging data, information on sociodemographic and clinical variables was obtained from physical and electronic medical records. The researchers collecting this information were unaware of the imaging findings. The following data were recorded: age, sex, use of invasive mechanical ventilation support, laboratory measurements including C-Reactive Protein (CRP), leucogram, platelet count, Alanine Transaminase (ALT), Aspartate Aminotransferase (AST), urea and creatinine levels. Additionally, the presence of medical comorbidities such as Diabetes Mellitus (DM), systemic arterial hypertension (SAH), coronary artery disease, need for hemodialysis, and deep vein thrombosis were documented. The assessment of laboratory test results was conducted according to specific values used by the hospitals laboratories, with the following normal ranges: white blood cell count from 3,500 to 11,000, platelets from 150,000 to 450,000, AST up to 34 U/L, ALT up to 55 U/L, total bilirubin up to 1.2 mg/dL, INR up to 1.2, urea up to 55 mg/dL, creatinine up to 1.2 mg/dL, CRP up to 5 mg/dL, fibrinogen up to 400 mg/dL, and LDH up to 220 mg/dL.The outcomes were in-hospital mortality due to COVID-19 and hospital discharge.

Statistical Analysis

Categorical variables were described as frequency (%), while non-categorical variables were presented as mean with standard deviation. Correlation between categorical variables and the outcome (death) was performed using Fisher's exact test or chi-square test, according to data characteristic for each categorical variable. The MedCalc software was used for analysis and a $p < 0.05$ were considered significant.

Ethical Considerations

This study was conducted in accordance with the principles of the Declaration of Helsinki. The hospital's Research Ethics Committee approved the research protocol, and written informed consent was obtained from all participating patients or their legally authorized representatives.

Results

During the study period, abdominal ultrasound was conducted on 61 patients. However, incomplete data in medical records led to the exclusion of two patients. The remaining 59 patients (with a mean age of 60 ± 15 years) were included in the study; of these, 36 (61%) were male and 48 (81%) were admitted to the Intensive Care Unit (ICU). The characteristics of this study population, who underwent ultrasound, are detailed in Table 1.

The most prevalent ultrasonographic findings included hepatic periportal thickening in 39 patients (66%), hepatic steatosis in 30 patients (51%), signs of chronic liver disease in 21 patients (36%), ascites in 15 patients (25%), and hepatomegaly in 6 patients (10%). An example of periportal thickening is illustrated. Seven patients were excluded from gallbladder evaluation due to post-cholecystectomy status or inadequate gallbladder distention during the examination. Among the 52 patients analyzed for gallbladder condition, 22 (42%) exhibited abnormalities, including changes in parietal and biliary content. Specifically, signs of gallbladder bile stasis were noted in 19 patients (36%), wall thickening in 9 (17%), and the presence of gallstones in 5 (10%). No signs of inflammation were observed in the pericholecystic fat, nor were there indications of acute cholecystitis. These findings are depicted. Of the 59 patients evaluated, 28 (47%) succumbed. In the univariate analysis considering demographic, clinical, and ultrasonographic findings (as shown in Table 2), only changes in gallbladder wall or bile content (excluding the presence of gallstones), the need for mechanical ventilation, the requirement for hemodialysis, and abnormal levels of creatinine, platelets, and leukocytes were significant.

Patient Characteristics		
Variable	Mean ± Standard Deviation or Frequency	
Age	60.85±15.1	
Sex	Male 36(61%); Female 23(39%)	
Local	ICU 48(81.4%); Nursery 11(18.6%)	
Outcome	Death 28(47.5%)	
Need of mechanical ventilation during hospital admission	38(64.4%)	
Median number of days to US since hospital admission (interquartile range)	5 (3 to 14)	
Obesity (54 patients with this information)	25 (46.3%)	
Need of hemodialysis during hospital admission	24 (40.7%)	
Previous hepatopathy	11 (18.6%)	
Kidney disease (57 with this information)	25 (42.4%)	
Presence of Deep vein Thrombosis	20 (33.9%)	
Ultrasonographic findings		
Ascites	15 (35.4%)	
Hepatic steatosis	30 (50.8%)	
Chronic hepatic disease	21 (35.6%)	
Portal Hypertension	8 (13.6%)	
Periportal thickening	39 (66.1%)	
Splenomegaly	10 (16.9%)	
Gallbladder (52 analyzed patients)	Gallbladder stones	5 (9.6%)
	Biliary sludge	19 (36.5%)
	Gallbladder wall thickening	9 (17.3%)

Table 1: Patient characteristics and ultrasonographic findings.

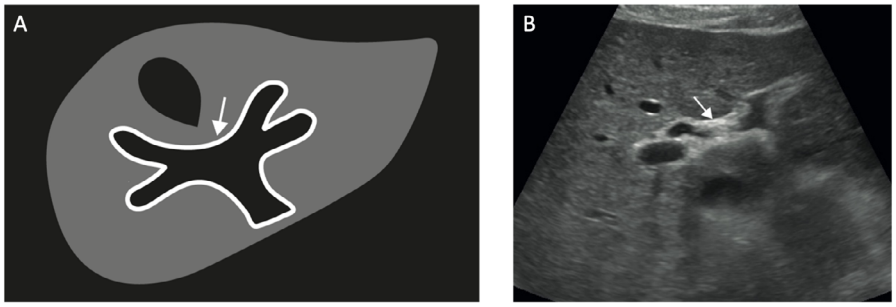

Figure 1: Periportal thickening in a patient with severe COVID-19. (A) Representation of a liver with periportal thickening on ultrasound (white arrow). (B) Ultrasound study demonstrating periportal thickening (white arrow).

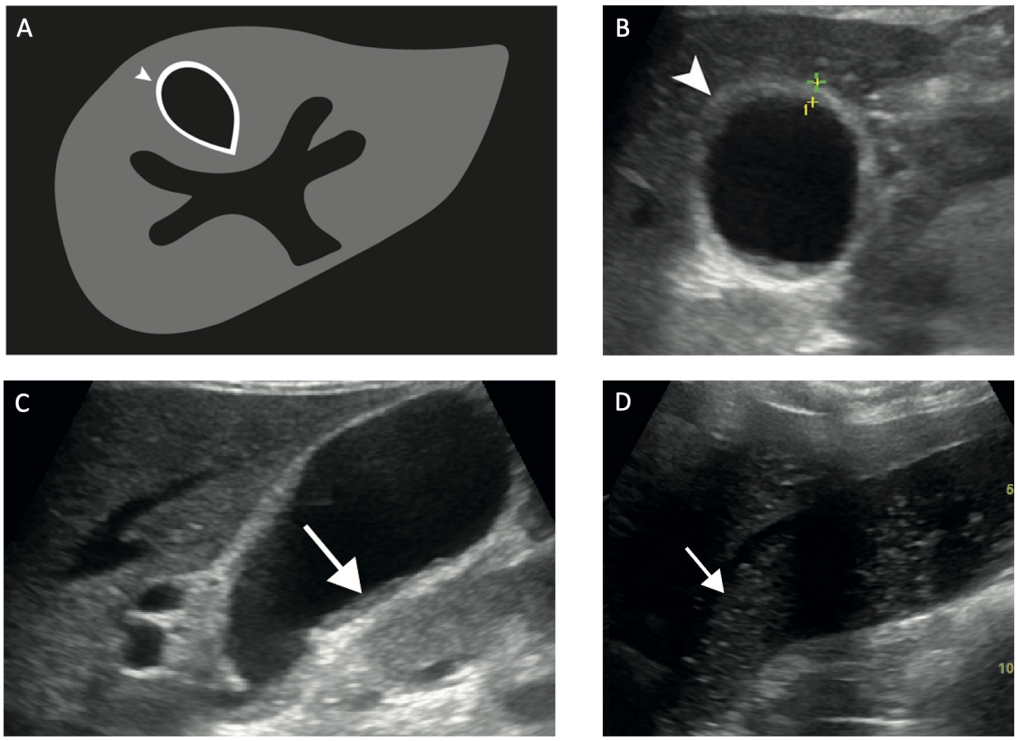

Figure 2: Signs of biliary abnormalities in individuals admitted to the ICU for severe COVID19: (A) Representation of gallbladder parietal thickening on ultrasound. In (B), (C), and (D), the gallbladder exhibits thickened walls (indicated by arrowheads) and dense bile content (indicated by white arrows).

Ultrasonographic findings		**Outcome**		**p-value**
		Hospital discharge (%)	Death (%)	
Ascites	Yes	6 (40.0)	9 (60.0)	0.260(*)
	No	25 (56.8)	19 (43.2)	
Hepatic steatosis	Yes	18 (60.0)	12 (40.0)	0.243(*)
	No	13 (44.8)	26 (55.2)	
Chronic hepatic disease	Yes	9 (42.9)	12 (57.1)	0.268(*)
	No	22 (57.9)	16 (42.1)	
Portal Hypertension	Yes	2 (25.0)	6 (75.0)	0.134(**)
	No	29 (56.9)	22 (43.1)	
Periportal thickening	Yes	18 (46.2)	21 (53.8)	0.170(*)
	No	13 (65.0)	7 (35.0)	
Gallbladder stones	Yes	2(40.0)	3(60.0)	1.000(**)
	No	23(50.0)	23(50.0)	
Biliary sludge	Yes	6 (31.6)	13 (68.4)	0.055(*)
	No	19(59.4)	13(40.6)	

Gallbladder wall thickening	Yes	1 (11.1)	8 (88.9)	**0.024(**)**
	No	24 (57.1)	19 (42.9)	
Splenomegaly	Yes	6 (60.0)	4 (40.0)	0.607
	No	24 (51.1)	23 (48.9)	
Laboratory findings		**Outcome**		**p-value**
		Hospital discharge (%)	Death (%)	
C-reactive protein test	Yes	23(47.9)	25(52.1)	(**)0.610
	No	3(75.0)	1(25.0)	
Abnormal leukocytes count	Yes	10(37.0)	17(63.0)	**(*)0.016**
	No	17(70.8)	7(29.2)	
Abnormal Platelets count	Yes	6(33.3)	12(66.7)	**(*)0.038**
	No	21(63.60	12(36.4)	
Abnormal Creatinine	Yes	10(35.7)	18(62.3)	**(*)0.019**
	No	17(68.0)	8(32.0)	
Abnormal liver enzymes	Yes	14(48.3)	15(51.7)	(*)0.644
	No	11(55.0)	9(45.0)	
Comorbidities		**Outcome**		**p-value**
		Hospital discharge (%)	Death (%)	
Obesity	Yes	13(52.0)	12(48.0)	(*)0.984
	No	15(51.7)	14(48.3)	
Need of hemodialysis during hospital admission	Yes	7(29.2)	17(70.8)	**(*)0.003**
	No	24(68.6)	11(31.4)	
Presence of Deep vein Thrombosis	Yes	10(50.0)	10(50.0)	(*)0.779
	No	21(53.8)	18(46.2)	
Previous hepatopathy	Yes	6(54.5)	5(45.5)	(*)0.883
	No	25(52.1)	23(47.9)	

Legend: *- Chi-square test. **- Fisher's exact test

Table 2: Univariate analysis for ultrasonographic findings and patient's data with death as outcome.

Discussion

This study portrayed hepatobiliary ultrasound alterations among hospitalized patients suffering from severe COVID-19. Periportal thickening, hepatic steatosis, signs of chronic liver disease, ascites, hepatomegaly, gallbladder bile stasis, gallbladder wall-thickening, and gallstones were the main findings. Cholestasis and thickening of the gallbladder wall were associated with higher mortality from severe COVID-19. Some limitations were encountered in this study. Notably, the sample size was restricted due to the considerable time required for donning and removing personal protective equipment, in addition to stringent protocols for minimizing the risk of transmission to the clinical team during US examination of critically ill SARS-CoV-2 patients. Additionally, incomplete medical records led to some missing data, which limited the clinicoradiological correlation. For these reasons, we did not perform logistic regression with significant variables due to the limited sample size, which could lead to overfitting of the analysis. Nevertheless, despite these challenges, the study was able to document abdominal manifestations in patients with severe COVID-19. Autopsy studies and in vitro experiments have demonstrated that SARS-CoV-2 attaches to ACE2 receptors, which are expressed in both hepatocytes and cholangiocytes within the liver, as well as in bile duct epithelial cells. This expression pattern may be linked to severe COVID-19 cases, where an exacerbated immune response associated with cytokine storms may play a

role in the pathophysiology of liver damage and hepatobiliary complications [9,11-13].

Gallbladder bile stasis, gallbladder wall thickening, and calculi have been reported in COVID patients. [8,27,29-32] These biliary abnormalities were identified in our study, and it was observed that patients with cholestasis and gallbladder wall-thickening had a higher mortality. Post-mortem examinations studies have reported cholestasis with bile plugs in the canaliculi and nuclear pleomorphism of cholangiocytes in severe COVID-19, which might be related to these imaging findings. [29,33] Several investigations have reported the potential association of SARS-CoV-2 with acute manifestations affecting the gallbladder, mimicking or even triggering acute cholecystitis. [30,31,34,35] There are hypotheses that these alterations may be related to an exacerbated inflammatory response of the organism and vascular thrombosis, [31] or even due to viral tropism for cholangiocytes. [30,31,34,35] However, no features of acute cholecystitis were found in our series, although other changes in the gallbladder were observed. Gallbladder wall thickening is not exclusively associated with primary gallbladder disorders but is often observed in patients with hepatitis, dengue, sepsis, and extracholecystic inflammation. The precise pathophysiological mechanisms remain to be fully elucidated; however, they are thought to involve increased capillary permeability, elevated portal venous pressure, systemic hypertension, reduced osmotic pressure, extension of inflammatory processes, immune responses, or a combination of these factors [36-39].

In this study, periportal thickening was the most common abdominal US finding. Periportal thickening is usually related to edema in the context of acute illness and has already been reported in magnetic resonance imaging and computed tomography. [5,29,40] Recent research corroborates our findings: periportal edema was commonly observed in children with COVID-19 and Multisystem Inflammatory Syndrome (MIS-C).[41] Post-mortem histological specimens have shown centrilobular congestion as the most frequent feature, possibly attributed to shock; lymphocytic infiltrate in the periportal zone was also found in several analyses. [33] Such histological changes may be related to this imaging finding. According to Revzin et al., the liver was the most frequently damaged organ outside of those of the respiratory system in COVID-19. Although the likely mechanism is multifactorial, it is believed that direct viral infection causing damage to cholangiocytes and hepatocytes, immune-mediated injury, vascular alterations with microthrombosis of hepatic sinusoids and generalized coagulopathy, as well as drug-induced hepatotoxicity are important contributing factors. [5,42] However, it is also important to note that hepatic alterations have previously been found in other infectious processes, such as hepatitis A, B, and C viruses, dengue virus, and the other two highly pathogenic coronaviruses – severe acute respiratory syndrome coronavirus (SARS-CoV) and the Middle East respiratory syndrome coronavirus (MERS-CoV) [36-38,42].

Signs of acute and chronic liver disease, ascites, and hepatomegaly were also identified in our study and recent studies [8,27,32,43]. These may be related to previous, worsened, or acquired conditions after COVID-19. [5,8,27,32,43] Spogis et al. revealed that for most hospitalized COVID-19 patients, mild to moderate elevation of liver enzymes (<10 times the upper limit of normal) caused little concern; nevertheless, in critically ill patients, bedside US is a highly effective tool for evaluating diverse patterns of liver complications,[8] corroborating our findings.

Although the explanation for our findings is not yet well defined, it is crucial to identify these changes, as they may be associated with greater severity of the condition or even greater risk of death. Previous investigations have highlighted the potential utility of bedside abdominal US as a valuable tool for identifying various types of complications related to cholestatic, vascular or inflammatory processes in critically ill patients with COVID-19, which may be associated with increased mortality risk. [8,32] Our study also revealed that some abdominal US abnormalities were associated with a higher risk of death. The prompt identification of these findings through bedside US could help diagnose and prevent complications, potentially improving clinical practice.

In summary, from a clinical standpoint, the ultrasound findings could aid in the prompt identification and meticulous surveillance of hepatic function, as well as in developing focused treatment and safeguarding measures in severe COVID-19 patients. Additionally, patients with cholestasis and gallbladder wall-thickening had a higher mortality, and these ultrasonographic findings can be used as a prognostic factor. However, subsequent studies should carefully investigate this possibility.

Ethics Approval Statement: The study was approved by the Research Ethics Committee of the Hospital das Clínicas of the Federal University of Pernambuco (CAAE: 34736620.6.0000.8807) and informed consent was obtained after being provided information regarding the study.

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