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A retrospective study of COVID-19 in patients with metabolic dysfunction-associated fatty liver disease (MAFLD) in Saudi Arabia

Mesk Saleh Ali Ghulais[1,2], Hasni Idayu Saidi[1,*], Huzwah Khaza'ai[1], Khaled Belal[3], Ummi Nadira Daut[4]. AbdulRahman Muthanna[1,5] & Nurliyana Najwa Md Razip[1,*]

[1]*Department of Biomedical Sciences, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, 43400 Serdang, Selangor, Malaysia.*
[2]*Laboratory Department, Almoosa Health Group, 7887 Dhahran Road, Al-Ahsa, Eastern Province, Saudi Arabia.*
[3]*Faculty of Medicine, Benha University, Al Nadi Al Ryadi Street, Benha, Al-Qalyubia Gorvrnorate, 13511, Egypt.*
[4]*Department of Medicine, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, 43400 Serdang, Selangor, Malaysia.*
[5]*Office of Postgraduate Studies, UCSI University, 1 Jalan UCSI, UCSI Heights (Taman Connaught), Cheras 56000, Kuala Lumpur, Malaysia.*

**Correspondence:* hasniidayu@upm.edu.my and nurliyananajwa@upm.edu.my

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ABSTRACT

Metabolic Dysfunction-Associated Fatty Liver Disease (MAFLD) has emerged as a significant comorbidity in COVID-19 patients. This retrospective case-control study included 224 COVID-19 patients (112 with MAFLD and 112 without MAFLD) for clinical and biochemical evaluation. Data collection followed a consecutive sampling protocol was performed using a random number generator on the list of eligible patients, incorporating all patients who met the inclusion criteria during the study period to ensure a representative and unbiased clinical sample. MAFLD patients demonstrated considerably worse clinical profiles compared to controls, with higher obesity rates (78% vs. 22%), prolonged hospitalization (84% vs. 16%), and more severe COVID-19 presentations (45% vs. 55%). During infection, significant differences were observed in AST, CRP, HSI, and AST/ALT ratio (p<0.05), while post-infection findings revealed significant changes in AST, PLT, PTT, and HIS (p<0.05), reflecting notable hepatic and hematological disruption. Multivariate logistic regression identified several independent risk factors influencing clinical outcomes. Saudi nationality was a significant predictor (adjOR = 0.289; p = 0.027), while hospital admission carried the highest associated risk (adjOR = 8.315; p < 0.001). COVID-19 severity also remained an independent contributing factor (adjOR = 0.291; p = 0.010). Among post-infection laboratory markers, both platelet count (adjOR = 1.003; p = 0.028) and the AST/ALT ratio (adjOR = 2.674; p = 0.018) were confirmed as independent variables influencing overall outcome. The clinical burden within the MAFLD cohort was substantial, with a mortality rate of 31.3% (35/112) and a recovery rate of only 68.8% (77/112), both significantly lower than in the control group. Notably, MAFLD alone was not found to be directly life-threatening; rather, COVID-19 severity remained the primary driver of adverse outcomes. In conclusion, the study confirms MAFLD as an important prognostic factor in COVID-19 patients, highlighting the need of clinical management for this high-risk population during pandemics.

Keywords: *COVID-19; comorbidity; infection; liver injury and MAFLD*

INTRODUCTION

The condition initially referred to as "novel coronavirus pneumonia" caused by a newly identified coronavirus, was first reported in Wuhan, China, in December 2019. Subsequently named Coronavirus Disease 2019 (COVID-19) by the World Health Organization (WHO) on February 11, 2020, when pandemic began. The causative agent of COVID-19 is the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) designated as a Class B infectious disease (Wang et al., 2020). COVID-19 has had a significant impact on cities across the world. The consequences of the COVID-19 epidemic in three

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major cities worldwide, namely New York City, London, and Tokyo, have demonstrated similarities and differences in the experiences of these global capitals. The United States (US) has recorded the most significant total number of cases globally, surpassing 12.9 million, while India and Brazil have reported 9.3 million and 6.2 million cases, respectively. The United Kingdom recorded almost 1.6 million cases, but Japan reported less than 140,000 cases (Marcotullio & Schmeltz, 2021). By February 2020, China had reported, 42,708 cases and 1,017 deaths, while only 393 cases and one death reported by 24 other countries (Okhowat, 2022). The number of confirmed COVID-19 cases in Saudi Arabia significantly increased, from one case on March 2, 2020, to 101,914 cases on June 7, 2020. The average daily count of new cases was 1,039. The trend test yielded a very significant result, with a p-value < 0.05. Despite an increase in the daily count of newly confirmed COVID-19 cases, the number of reported daily active cases has started to level off two months after the beginning of the pandemic in the country (Alyami et al., 2020)

An epidemiological study found a significant influence of COVID-19 on liver function and its relationship to its severity. Multiple investigations have documented abnormal liver function tests (LFTs) in patients diagnosed with COVID-19, highlighting the virus's systemic effects beyond the respiratory system. A comprehensive retrospective cohort analysis of 2,073 patients diagnosed with COVID-19 in Wuhan, China, was conducted. This analysis found that many, but not all, COVID-19s exhibited abnormal liver function test results, indicating a high prevalence of liver disease (Ding et al., 2021). Additionally, data from a tertiary care center in Mexico City, showed that 40.6% of the 432 participants had a fatty liver visible on computed tomography (CT). The average age of the group was 51 ± 13-year-old, with the majority being male (Campos-Murguía et al., 2021). Observational studies on COVID-19 patients with Chronic Liver Disease (CLD) reveal significant correlations between the elevation of the liver enzymes, specifically aspartate transaminase (AST) and alanine transaminase (ALT) (Sharma et al., 2021).

The transition from acute COVID-19 to sustained liver injury in MAFLD remains under investigation, though two primary mechanisms are suspected. First, hepatic ACE2 expression, the primary entry receptor for SARS-CoV-2 is significantly higher in patients with metabolic dysfunction (Webb et al., 2020; Marjot et al., 2021). Second, the synergy between the COVID-19 'cytokine storm' and the chronic inflammatory milieu of MAFLD likely accelerates hepatocellular damage (Eslam et al., 2020).

The pathways contributing to liver injury in COVID-19 involve both direct and indirect mechanisms linked to the interaction of SARS-CoV-2 with angiotensin-converting enzyme 2 (ACE2) receptors. SARS-CoV-2 enters hepatocytes via ACE2 receptors, potentially causing directly liver injury. These interactions result in systemic adverse effects with molecular initiating events (MIEs) originating in other organs that eventually affect the liver (Vinken, 2021). SARS-CoV-2 enters hepatocytes via angiotensin-converting enzyme 2 (ACE2) receptors, potentially causing direct liver injury. It is necessary to investigate whether SARS-CoV-2 infection exacerbates cholestasis in individuals with primary biliary cholangitis, given the presence of ACE2 receptors on cholangiocytes' surfaces (Zhang et al., 2020).

However, research is also exploring whether pre-existing liver injury can worsen COVID-19 infections. This potential worsening may be due to the fact that pre-existing injury often involves metabolic disorders that enhance comorbidities such as diabetes and obesity. MAFLD is diagnosed when more than 5% of liver cells show steatosis, which is determined by examining tissue samples or measuring the proton density fat fraction. This diagnosis applies to individuals who do not consume excessive amounts of alcohol and do not have any other underlying cause for the presence of steatosis (Parks et al., 2005). Hepatic steatosis, characterised by the accumulation of lipids in liver cells, predominantly hepatocytes, represents the initial stage of MAFLD progression. The condition has the potential to advance to metabolic dysfunction associated with steatohepatitis (MASH), a metabolic disorder marked by inflammation and hepatocellular damage resulting from fat accumulation, ultimately leading to the development of advanced liver disease. The diagnosis and prognosis of all patients necessitate liver biopsies (Angulo et al., 1999). The current guidelines state that to be diagnosed with MAFLD, hepatic steatosis must be present along with three criteria: metabolic dysregulation, type 2 diabetes mellitus, or overweight/obesity (Eslam et al., 2020). So, a single diagnostic laboratory test is insufficient to establish the diagnosis of MAFLD. Rather, it relies on identifying a unique combination of histological characteristics in patients with insulin resistance, visceral adiposity, obesity, T2DM or insulin resistance (Farrell et al., 2005).

Globally, the prevalence of MAFLD is estimated to be 25.24% (95% CI: 22.10-28.65), with significantly higher rates observed in the Middle East and South America, and considerably lower rates in Africa. This condition strongly correlates with the characteristic features of metabolic syndrome (Younossi et al., 2016). Moreover, studies have shown that obesity was observed to increase the risk of severe illness in MAFLD patients by six times after controlling confounding variables, suggesting a combined effect of both obesity and MAFLD when assessing the risk of severe COVID-19 (Hussain et al., 2020). It is also important to note that the resulting liver damage in hospitalized COVID-19 patients can be a result of the SARS-CoV-2 virus directly affecting the patient or from the medications used to treat the infection, occurring in up to 50% of admissions (Vinken, 2021). In another study at the Yale Pediatric Obesity Clinic, researchers evaluated participants from the Yale Study of Prediabetes in Youth to investigate the pathophysiology of prediabetes in youth. The study compared data from before the COVID-19 pandemic (January 2017 to November 2019) with data from during the pandemic (August 2020 to May 2022) in Wuhan, China. The study revealed a significant increase in the prevalence of MAFLD from 36.2% to 60.9% during the pandemic, and the severity of MAFLD in patients changed noticeably during this time (Slusher et al., 2023). The mortality rate linked to liver-related causes was considerably higher (28.6%, p <0.001) among patients with pre-existing decompensated liver illness (Hartl et al., 2022).

Ultimately, continuous scientific and ethical evidence supports the necessity of sustained research efforts focused on MAFLD/MASH. Identification of MAFLD has been associated with an elevated risk of exacerbated COVID-19 symptoms, emphasising the urgency of implementing measures to mitigate disease severity (Alkhouri et al., 2020). The presence of MAFLD has been linked to elevated COVID-19 severity, unfavourable outcomes, and pulmonary thrombosis (Vrsaljko et al., 2022).

This study aims to evaluate the risk factors associated with MAFLD in hospitalized COVID-19 patients, particularly focusing on how MAFLD correlates with heightened susceptibility to severe illness based on the interpretation of biochemical parameters. A primary objective is to assess the prevalence, clinical characteristics, and predictors of COVDI-19 patients both with and without pre-existing MAFLD. Furthermore, the research will examine the role of key metabolic comorbidities such as diabetes, cardiovascular disease and chronic respiratory conditions, in the progression of MAFLD and their subsequent association with COVID-19 complications

METHODOLOGY

Study design, sampling and participants

An analytic observational retrospective case-control study based on reviewing the laboratory results of confirmed positive SARS-CoV-2 patients was conducted at King Fahad Hospital, Al Ahsa City, Saudi Arabia, during the year 2020. The patients were divided into two groups with and without MAFLD as a representation of case and control groups respectively. The inclusion criteria were based on the adults' patients who were 18 years old and above, positive SARS-CoV-2 screening using RT-PCR and exhibit mild to severe symptoms. For the cases group, the subjects that were diagnosed with MAFLD must have hepatic steatosis present along with either metabolic dysregulation, T2DM, or overweight/obesity as well as evaluated by the physician in a recorded pre-existing medical condition or the ultrasound report of hepatic steatosis which indicates MAFLD. For the controls group of without MAFLD. The availability of laboratory results within 14 days of positive SARS-CoV-2 based on RT-PCR screening during an infection as well as post-infection laboratory data were included following negative SARS-CoV-2 screening using RT-PCR before patient discharge. Whereas patients under 18 years old, any missing clinical data or laboratory investigations in the hospital information system or medical records were excluded. A consecutive sampling technique was adopted in the current study. Information on the admitted patients with positive SARS-CoV-2 was extracted and correlated with laboratory investigation through a valid electronic medical system. The patient admission with positive SARS-CoV-2 was verified via cross-referencing with the medical records file. Mortality was defined as any death occurring during the hospital stay as recorded in the clinical EHR; the formal WHO death certification criteria and verbal autopsy protocols were not applied to this analysis.

The reference sample size calculation formula for unmatched case-control with equal cases and controls was used to calculate the sample size. Using a two-sided alpha of 0.05, power of 80%, and an estimated 20% difference in exposure between cases and controls, the required sample size was calculated as 112 patients per group (total N=224).

$$n = \frac{\left\{1.96*\sqrt{(1+1)*0.5*0.5}\ \ (-0.842)\sqrt{(1*0.606*0.92)+(0.5*0.5)}\right\}^2}{1*(0.394-0.606)2}$$

Internal validity was maintained by selecting controls from the same source population and study period as the cases. While baseline characteristics were assessed for parity, any residual confounding was further addressed through multivariate logistic regression. This allowed for the statistical isolation of MAFLD-related outcomes by controlling for covariant factors identified during the baseline assessment. Patients with missing data for key variables were excluded listwise. The number of missing observations for each variable is reported in Table 1.

Data collection

Information on the admitted patients with positive SARS-CoV-2 was extracted and correlated with laboratory investigation through a valid electronic medical system. The information includes socio-demographic (age, gender and nationality), body mass index (BMI), comorbidity disease, hospital admission, COVID-19 severity, patient status and laboratory test. Whereby, the laboratory test includes liver function tests (LFTs) such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TBIL), direct bilirubin (DBIL), total protein (TP), and albumin (ALB), hemoglobin (Hb), red blood cell count (RBC), white blood cell count (WBC), platelet count (PLT), prothrombin time (PT), partial thromboplastin time (PTT), D-dimer, C-reactive protein (CRP) and ferritin were conducted in this research. The ratio of biochemical properties such as hepatic steatosis index (HSI) is from the hepatic ultrasonography and evaluation of the lifestyle modifications which were recognized for MAFLD diagnostic tool (Priego-Parra et al., 2024). MAFLD was defined using a standardized operational protocol based on the international consensus criteria. Patients were included if they presented with hepatic steatosis (detected by abdominal ultrasound or recorded clinical diagnosis supported by imaging) in addition to one or more of the following: overweight/obesity (BMI > 23kg/m^2) or ≥2 metabolic risk abnormalities., Type 2 Diabetes Mellitus, or metabolic dysregulation (defined by the presence of at least two metabolic

risk factors such as hypertension, dyslipidemia, or pre-diabetes). This 'positive' diagnostic framework ensured that the inclusion criteria remained consistent regardless of other concomitant conditions or alcohol consumption (Eslam, et al., 2020). Nonetheless, according to the clinical final diagnosis history recorded by the treating physician, MAFLD and other pre-existing medical conditions were included in the inclusion criteria. The (HSI) is an efficient screening tool for MAFLD that may be utilized to select individuals for liver ultrasonography and determine the need for lifestyle modifications. Calculation formulas utilized in the assessment of biomarker indicators serve as predictive tools for MAFLD. HSI was calculated based on 8 × (ALT/AST ratio) + BMI (+2 if female). An HSI score >36 was utilized as the highly specific cutoff for the presence of hepatic steatosis, as per established literature (Lee et al., 2010). Patients with documented alcoholic liver disease, viral hepatitis, or other chronic liver diseases were excluded from both groups.

The Health Electronic Surveillance Network (HESN) system, an electronic platform utilized by the Ministry of Health in Saudi Arabia, was used to aggregate data for the verification of COVID-19 cases and to streamline the reporting process. Laboratory results, demographic data, and clinical interpretations were extracted from the OASIS hospital information system used by King Fahad Hospital. The laboratory results were exported alongside with SARS-CoV-2 test using polymerase chain reaction (PCR) integrated in the HESN system to confirm the accuracy of the extracted patient's data. Also, laboratory results were included in if collected within 14 days of a positive PCR test for 'during infection' measurements, and within 14 days of a negative PCR test for 'after infection' measurements. The World Health Organization (WHO) defines a COVID-19 death as one resulting from a clinically compatible illness in a probable or confirmed COVID-19 case, unless there is a clear alternative cause of death that cannot be related to the disease, such as trauma. The WHO states that there should be no period of complete recovery from COVID-19 between illness and death (Feyissa et al., 2021). If a death happened due to COVID 19 infection, it was deemed a COVID 19-related death.

Patients diagnosed with fatty liver were identified utilizing Picture Archiving and Communication System (PACS). PACS is a comprehensive system comprising hardware, software, and networks designed to store, retrieve, and distribute medical images. Widely employed in the fields of radiology, cardiology, and pathology, PACS converts medical imaging data from X-ray, magnetic resonance imaging (MRI), and ultrasound machines into a digital format and stores them in a centralized database. The control group comprised patients with imaging-confirmed absence of hepatic steatosis via abdominal ultrasound, thereby minimizing potential confounding from undiagnosed metabolic liver disease. Data was collected and entered the master sheet using Microsoft Excel 2016. Verification via cross-referencing with the hard copy of the patient file in the medical record was also performed. To correlate the diagnosis that were documented by physician in patient final report for MAFLD, the PACS data was verified during the year 2020 by radiologist, which it was existing with patient COVID-19 infection data. The final outcomes of PACS report did not specify the severity of hepatic steatosis, yet indicating simply the homogeneous bright echogenicity associated with MAFLD.

Data analysis

Data was analyzed using IBM SPSS Statistics for Windows, Version 27.0. Normality of continuous variables was assessed using the Shapiro-Wilk test. Descriptive objective variables were represented as percentiles and frequencies. The median and interquartile range (IQR) were calculated for non-normally distributed continuous variables. The Mann-Whitney test was utilized to compare between cases and control in COVID-19 patients. The Chi-Square (c^2) test was utilized to examine the relationship between pre-existing MAFLD and COVID-19 patients with the outcomes. To assess statistical interaction, the binary logistic regression was deployed in this study to assess main predictor variables and their product terms. The predictor variables considered from the univariate logistic regression analysis. A *p*-value of < 0.05 was considered statistically significant in all statistical analyses.

For all categorical variables included in the multivariate logistic regression models, reference categories were established a priori. Specifically, Saudi nationality, male gender, and home isolation status served as the reference groups (OR = 1.0) against which the odds of clinical recovery were compared. This allowed for a precise quantification of the relative risk associated with non-Saudi status, female gender, and hospital admission, respectively.

RESULTS

Table 1 displays details of the study participants' baseline characteristics between case and control groups. The current retrospective study involved 224 patients (112 in each group), which met the inclusion criteria stated by the study design. A significant proportion of affected individuals were Saudi Arabian citizens, with 70.5% in the control group and 89.3% in the case group ($p < 0.05$). Gender distribution showed 63.4% females in the control group versus 50.9% in the case group, while males comprised 49.1% in the case group and 36.6% in the control group; however, gender differences were not statistically significant ($p = 0.059$). Age, depicted as a risk factor, had median (IQR) values of 55 (17.5) years for cases and 50 (15) years for controls, with no significant difference ($p = 0.131$). BMI differed significantly between groups, with a median of 37.00 kg/m² (IQR 11.50) in cases versus 30.80 kg/m² (IQR 14.85) in controls ($p < 0.05$). Comorbidities were prevalent in both groups, with 88% in controls and 83% in cases, showing no significant difference ($p = 0.176$). According to the Ministry of Health Saudi Arabia guidelines, the severity of COVID-19 cases can be classified as either mild or moderate or severe depending on symptoms, the length and extent of the

hospital admission (Ministry of Health Saudi Arabia, 2020). Severity and mortality data revealed a significant difference (p = 0.032), as severe cases accounted for 61% in the case group and 75% in the control group. Hospitalization rates were significantly higher (p < 0.001) in the case group, with 43% admitted compared to 8% of controls, and mortality was also significantly higher (p < 0.05), with 31% of deceased patients exclusively diagnosed with MAFLD.

Table 1

Sociodemographic and clinical characteristics of COVID-19 patients with (cases) or without MAFLD (controls)

Sociodemographic characteristics	**Cases (with MAFLD)**		**Control (without MAFLD)**		**Z/χ^2**	***p*-value**
	n (%)	**Median (IQR)**	**n (%)**	**Median (IQR)**		
Age		55.00 (17.50)		50.00 (15.00)	-1.512[a]	0.109
<40	26 (85)		15(15)			
40-59	47 (49)		50 (51)			
>60	39 (45)		47 (55)			
[#]BMI	59	37.00 (11.50)	32	30.80 (14.85)	-3.359[a]	<0.001*
Underweight	NA	NA	NA	NA		
Normal	3 (23)		10 (77)			
Overweight	10 (53)		9 (47)			
Obesity	46 (78)		13 (22)			
Gender						
Male	57 (45)		71 (55)		3.573[b]	0.059
Female	55 (57)		41 (43)			
Nationality						
Saudi	100 (56)		79 (44)		12.264[b]	<0.001*
Non-Saudi	12 (27)		33 (73)			
Presence of comorbidity disease						
Yes	93 (48)		100 (52)		1.835[b]	0.177
No	19 (61)		12 (39)			
Hospital admission						
Admitted	48 (84)		9 (16)		35.792[b]	<0.001*
Home isolation	64 (38)		103 (62)			
COVID-19 severity						
Severe	69 (45)		84 (55)		4.640[b]	0.032*
Mild/moderate	43 (61)		28 (39)			
Patient status						
Deceased	35 (100)		0 (0)		41.481[b]	<0.001*
Recovered	77 (41)		112 (59)			

*Note: n: Sample size. IQR: Interquartile range. [a]: Mann-Whitney U test (z). [b]: Chi-square test (χ2). BMI: Body mass index. *Significant result at p<0.05. [#]BMI data is available for 59 cases and 32 controls only.*

Table 2 displays the association of laboratory measurements with (cases) or without MAFLD (controls) during and after infections of COVID-19. The outcomes show significant differences (P<0.05) between cases and controls in AST of during (22 U/L, IQR: 25 U/L) versus (34.00 U/L, IQR: 11.00U/L) and after infections (cases: 24.00, IQR: 19.00) versus (controls18.00, IQR: 25.00) respectively, PLT of after infections (cases: 204.00, IQR: 21410 ^ 9 /L versus controls: 255, IQR: 21810 ^ 9 /L, P<0.05), PTT of after infections (cases: 36.60, IQR: 24.40 versus controls: 34, IQR: 53.14, P<0.05). Wide interquartile range indicates presence of outliers or non-normal distribution. CRP of during infections (cases: 0.00,

IQR: 0.71 versus controls: 0.00, IQR: 9.95, P<0.05), HSI of during (cases: 50.00, IQR:17.95, versus controls: 39.50, IQR:11.80, P<0.05) and after infections (cases: 51.30, IQR: 24.95 versus controls: 42.60, IQR: 18.15, P<0.05) as well as AST/ALT ratio of during infections (cases: 0.80, IQR: 0.65 versus controls: 1.60, IQR:1.60, P<0.05).

Table 2

The association of laboratory measurements with (cases) and without MAFLD (controls) in COVID-19 patients

Variable	Cases (with MAFLD)		Controls (without MAFLD)		Z[a]	P	Reference Range/ Unit
	n (%)	Median (IQR)	n (%)	Median (IQR)			
Liver Function Test							
ALT *During infection COVID-19*	112 (50.0)	22.70 (31.00)	112 (50.0)	21.00 (25)	-0.089	0.929	10-35 U/L
ALT *After infection COVID-19*	110 (49.5)	31.00 (120.50)	112 (50.5)	16.00 (39.00)	-1.234	0.217	
AST *During infection COVID-19*	112 (50.0)	22.20 (20.05)	112 (50.0)	34.00 (11.00)	-2.351	0.019*	0-31 U/L
AST *After infection COVID-19*	111 (49.8)	24.00 (19.00)	112 (50.2)	18.00 (25.00)	-2.741	0.006*	
TBIL *During infection COVID-19*	107 (50.0)	8.50 (7.25)	107 (50.0)	10.50 (3.18)	-0.59	0.555	0-17 mmol/L
TBIL *After infection COVID-19*	103 (48.8)	19.70 (46.55)	108 (51.2)	10.50 (3.18)	-1.756	0.079	
DBIL *During infection COVID-19*	85 (51.2)	1.50 (3.93)	81 (48.8)	0.89 (3.28)	-0.232	0.816	0-5 mmol/L
DBIL *After infection COVID-19*	83 (51.9)	4.68 (23.14)	77 (48.1)	1.50 (4.92)	-1.774	0.076	
TP *During infection COVID-19*	98 (48.8)	68.00 (7.70)	103 (51.2)	58.00 (29.75)	-1.787	0.074	62-73 mmol/L
TP *After infection COVID-19*	84 (43.3)	62.00 (11.75)	110 (56.7)	62.00 (11.10)	-0.122	0.903	
ALB *During infection COVID-19*	99 (50.8)	34.30 (8.60)	96 (49.2)	26.00 (8.70)	-0.837	0.403	35-50 mmol/L
ALB *After infection COVID-19*	89 (46.4)	30.10 (11.85)	103 (53.6)	28.00 (3.50)	-1.131	0.258	

*Note: Laboratory values were available only for patients whom the test was clinically indicated.# CRP reference range 0-0.8 mg/dL as per King Fahad Hospital laboratory standards. Abbreviation: IQR: Interquartile range. [a]: Mann-Whitney U test. *Significant result at p<0.05. Abbreviations: ALT: Alanine transaminase, AST: Aspartate transaminase, TBIL: total bilirubin, DBIL: direct bilirubin, TP: total protein, ALB: albumin, Hb: hemoglobin, HCT: hematocrit, RBC: red blood cell, WBC: white blood cell, PLT: platelet count, PT: prothrombin time, PTT: partial thromboplastin. CRP: C-reactive protein.*

Table 2 (continued)

The association of laboratory measurements with (cases) and without MAFLD (controls) in COVID-19 patients

Variable	Cases (with MAFLD)		Controls (without MAFLD)		Z[a]	P	Reference Range/ Unit
	n (%)	Median (IQR)	n (%)	Median (IQR)			
Hematology Panels							
HB *During infection COVID-19*	111 (50.5)	10.90 (4.80)	109 (49.5)	9.00 (6.00)	-1.382	0.167	12-15 g/dL
HB *After infection COVID-19*	105 (49.5)	10.60 (4.80)	107 (50.5)	9.60 (5.05)	-1.334	0.182	
HCT *During infection COVID-19*	111 (50.5)	33.10 (13.95)	109 (49.5)	32.00 (17.40)	-0.358	0.720	36-46 %
HCT *After infection COVID-19*	105 (49.5)	31.00 (14.15)	107 (50.5)	35.00 (15.20)	-0.758	0.448	
RBC *During infection COVID-19*	111 (50.5)	4.43 (1.86)	109 (49.5)	5.10 (1.87)	-1.057	0.290	3.8-4.8 10 ^ 12/L
RBC *After infection COVID-19*	104 (49.3)	4.02 (2.21)	107 (50.7)	4.84 (2.31)	-0.801	0.423	
WBC *During infection COVID-19*	111 (50.5)	5.56 (2.33)	109 (49.5)	8.62 (6.56)	-0.339	0.735	4-10 10 ^ 9 /L
WBC *After infection COVID-19*	104 (49.3)	9.58 (9.87)	107 (50.7)	5.74 (4.81)	-1.258	0.208	
PLT *During infection COVID-19*	111 (50.5)	238.00 (157.50)	109 (49.5)	202.00 (146.00)	-0.515	0.607	130-400 10 ^ 9 /L
PLT *After infection COVID-19*	104 (49.5)	204.00 (214.00)	106 (50.5)	255.00 (218.00)	-3.706	<0.001*	
PT *During infection COVID-19*	66 (57.9)	12.40 (2.80)	48 (42.1)	12.10 (2.85)	-0.184	0.854	9.8-13.2 sec
PT *After infection COVID-19*	58 (59.8)	14.10 (21.40)	39 (40.2)	13.90 (3.20)	-0.857	0.391	
PTT *During infection COVID-19*	65 (59.1)	32.10 (5.70)	45 (40.9)	30.70 (13.00)	-0.416	0.677	26-36 sec
PTT *After infection COVID-19*	56 (58.9)	36.60 (24.40)	39 (41.1)	34.00 (53.15)	-3.636	<0.001*	

*Note: Laboratory values were available only for patients whom the test was clinically indicated.# CRP reference range 0-0.8 mg/dL as per King Fahad Hospital laboratory standards. Abbreviation:IQR: Interquartile range. [a]: Mann-Whitney U test. *Significant result at p<0.05. Abbreviations: ALT: Alanine transaminase, AST: Aspartate transaminase, TBIL: total bilirubin, DBIL: direct bilirubin, TP: total protein, ALB: albumin, Hb: hemoglobin, HCT: hematocrit, RBC: red blood cell, WBC: white blood cell, PLT: platelet count, PT: prothrombin time, PTT: partial thromboplastin. CRP: C-reactive protein.*

Table 2 (continued)

The association of laboratory measurements with (cases) and without MAFLD (controls) in COVID-19 patients

Variable	Cases (with MAFLD)		Controls (without MAFLD)		Z[a]	P	Reference Range/ Unit
	n (%)	Median (IQR)	n (%)	Median (IQR)			
Hematology Panels (continued)							
D-dimer *During infection COVID-19*	31 (44.3)	0.00 (0.16)	39 (55.7)	0.00 (1.30)	-0.816	0.415	0-0.49 mg/L FEU
D-dimer *After infection COVID-19*	22 (44.9)	0.00 (0.17)	27 (55.1)	0.00 (2.44)	-1.749	0.080	
Inflammatory markers							
CRP *During infection COVID-19*	35 (54.7)	0.00 (0.71)	29 (45.3)	0.00 (9.95)	-2.192	0.028*	#0-0.8 mg/dL
CRP *After infection COVID-19*	19 (57.6)	0.00 (0.00)	14 (42.4)	0.00 (1.70)	-0.401	0.688	
Ferritin *During infection COVID-19*	45 (39.8)	33.00 (536.50)	68 (60.2)	216.00 (136.35)	-1.111	0.266	11.1-264 ng/mL
Ferritin *After infection COVID-19*	18 (45.0)	0.00 (53.95)	22 (55.0)	0.00 (27.15)	-0.272	0.786	
HSI Index *During infection COVID-19*	60 (65.2)	50.00 (17.95)	32 (34.8)	39.50 (11.80)	-3.800	<0.001*	
HSI Index *After infection COVID-19*	60 (65.2)	51.30 (24.95)	32 (34.8)	42.60 (18.15)	-3.304	0.001*	
APRI Index *During infection COVID-19*	101 (48.8)	0.30 (0.50)	106 (51.2)	0.30 (0.45)	-1.931	0.054	<0.5
APRI Index *After infection COVID-19*	102 (49.3)	0.30 (0.90)	105 (50.7)	0.50 (0.45)	-0.310	0.756	
AST/ALT Ratio *During infection COVID-19*	111 (49.8)	0.80 (0.65)	112 (50.2)	1.60 (1.60)	-3.242	0.001*	
AST/ALT Ratio *After infection COVID-19*	110 (49.5)	0.80 (0.65)	112 (50.5)	2.10 (2.70)	-1.915	0.055	

*Note: Laboratory values were available only for patients whom the test was clinically indicated.# CRP reference range 0-0.8 mg/dL as per King Fahad Hospital laboratory standards. Abbreviation:IQR: Interquartile range. [a]: Mann-Whitney U test. *Significant result at p<0.05. Abbreviations: ALT: Alanine transaminase, AST: Aspartate transaminase, TBIL: total bilirubin, DBIL: direct bilirubin, TP: total protein, ALB: albumin, Hb: hemoglobin, HCT: hematocrit, RBC: red blood cell, WBC: white blood cell, PLT: platelet count, PT: prothrombin time, PTT: partial thromboplastin. CRP: C-reactive protein.*

Table 3 describes the associations between MAFLD in COVID-19 with socio-demographic factors, clinical characteristics, laboratory measurements, HSI index, APRI index and AST/ALT ratio outcomes using univariate logistic regression. The findings showcase the significant association such as BMI (OR:0.907, P<0.05) and Odd Ratio (OR) of 0.907 for BMI in relation to the primary outcome of clinical recovery, this indicates an inverse association where each

Table 3

The associations between MAFLD in COVID-19 with socio-demographic factors, clinical characteristics, laboratory measurements, HSI index, APRI index and AST/ALT ratio outcomes using univariate logistic regression

Variables	OR[a]	95% CI[b]	P-value
Age	1.013	0.995 – 1.031	0.162
BMI	0.907	0.850 – 0.969	0.004*
Gender			
Male	1.671	0.980 – 2.850	0.059
Female	Ref		
Nationality			
Saudi	0.287	0.139 – 0.592	0.001*
Non-Saudi	Ref		
Presence of comorbidity disease			
Yes	1.703	0.784 – 3.669	0.179
No	Ref		
Hospital admission			
Admitted	Ref		
Home isolation	9.400	4.117 – 21.154	<0.001*
COVID-19 severity			
Severe	0.535	0.302 – 0.948	0.032*
Mild/moderate	Ref		
Patient status			
Deceased	Ref		
Recovered	6.818	2.876 – 16.163	<0.001*
Liver Function Test			
ALT During infection of COVID-19	0.999	0.997 - 1.002	0.500
ALT After infection of COVID-19	0.999	0.996-1.001	0.290
AST During infection of COVID-19	1.000	0.999-1.001	0.528
AST After infection of COVID-19	0.999	0.997-1.001	0.313
TBIL During infection of COVID-19	0.770	0.993-1.010	0.770
TBIL After infection of COVID-19	0.984	0.970 - 0.998	0.028*
DBIL During infection of COVID-19	0.979	0.949-1.009	0.172

*Note: OR[a]-Unadjusted Odds ratio, 95% CI[b] – Confidence interval, *P-value shows when p is < 0.05.*

Table 3 (continued)

The associations between MAFLD in COVID-19 with socio-demographic factors, clinical characteristics, laboratory measurements, HSI index, APRI index and AST/ALT ratio outcomes using univariate logistic regression

Variables	OR[a]	95% CI[b]	P-value
Liver Function Test (continued)			
DBIL *After infection of COVID-19*	0.994	0.985-1.004	0.229
TP *During infection of COVID-19*	0.965	0.934-0.996	0.027*
TP *After infection of COVID-19*	1.00	1.000-1.000	0.566
ALB *During infection of COVID-19*	0.990	0.950-1.031	0.624
ALB *After infection of COVID-19*	1.001	0.997-1.006	0.536
Hematology Panels			
HB *During infection of COVID-19*	1.002	0.947-1.061	0.935
HB *After infection of COVID-19*	1.127	1.014-1.252	0.026*
HCT *During infection of COVID-19*	1.012	0.977-1.048	0.515
HCT *After infection of COVID-19*	1.012	0.980-1.045	0.480
RBC *During infection of COVID-19*	1.152	0.987-1.478	0.268
RBC *After infection of COVID-19*	1.189	0.915-1.545	0.194
WBC *During infection of COVID-19*	1.004	0.989-1.020	0.579
WBC *After infection of COVID-19*	1.001	0.983-1.019	0.942
PLT *During infection of COVID-19*	1.000	0.997-1.002	0.750
PLT *After infection of COVID-19*	1.003	1.002-1.005	<0.001*
PT *During infection of COVID-19*	0.983	0.896-1.080	0.725
PT *After infection of COVID-19*	0.930	0.858-1.009	0.079
PTT *During infection of COVID-19*	0.980	0.966-0.994	0.006*
PTT *After infection of COVID-19*	0.980	0.967-0.992	0.001*
D-dimer *During infection of COVID-19*	1.078	0.950-1.223	0.246
D-dimer *After infection of COVID-19*	0.973	0.826-1.144	0.737

*Note: OR[a]-Unadjusted Odds ratio, 95% CI[b] – Confidence interval, *P-value shows when p is < 0.05.*

Table 3 (continued)

The associations between MAFLD in COVID-19 with socio-demographic factors, clinical characteristics, laboratory measurements, HSI index, APRI index and AST/ALT ratio outcomes using univariate logistic regression

Variables	ORa	95% CIb	P-value
Inflammatory markers (continued)			
CRP *During infection of COVID-19*	1.012	0.978-1.047	0.499
CRP *After infection of COVID-19*	1.004	0.995-1.013	0.412
Ferritin *During infection of COVID-19*	1.000	1.000-1.000	0.725
Ferritin *After infection of COVID-19*	1.000	1.000-1.000	0.437
HSI Index *During infection of COVID-19*	0.972	0.960-0.985	<0.001*
HSI Index *After infection of COVID-19*	0.973	0.962-0.985	<0.001*
APRI Index *During infection of COVID-19*	0.988	0.953-1.024	0.502
APRI Index *After infection of COVID-19*	0.870	0.743-1.018	0.083
AST/ALT Ratio *During infection of COVID-19*	1.375	0.992-1.905	0.056
AST/ALT Ratio *After infection of COVID-19*	1.855	1.130-3.047	0.015

*Note: OR[a]-Unadjusted Odds ratio, 95% CI[b] – Confidence interval, *P-value shows when p is < 0.05.*

one-unit (<1 kg/m^2) increase in BMI was associated with a 9.3% reduction in the odds of recovery (1 -0.907 = 0.093). These findings suggest that higher BMI acts as a negative predictor for favourable clinical outcomes, due to the pro-inflammation and metabolic disorders associated with increased adiposity in COVID-19.

Saudi nationality serving as the reference category, the OR of 0.287 for Non-Saudi patients indicates a 71.3% reduction in the odds of achieving the outcome. This statistical finding highlights nationality as a significant covariate, which it shows an OR:0.287, ($p<0.05$). Meanwhile, hospital admission was 9.4, indicating that patients who were admitted had 9.4 times of mortality compared to those in home isolation. The severity of COVID-19 based on the hospital admission (OR: 9.4, $p<0.05$) and the severity of COVID-19 itself shows (OR: 0.535, $p<0.05$).

The association between COVID-19 severity and MAFLD status was characterized by an inverse relationship with recovery rate of (OR: 0.535). This explained that each one-unit increase in initial disease severity at 46.5% reduction in the odds of recovery within the study population. These data suggest that in the presence of metabolic dysfunction, the clinical threshold for recovery becomes significantly harder to reach as the initial COVID-19 presentation was worsen. TBIL of after infection (OR: 0.984, $p<0.05$) TP of during infection (OR: 0.965, $p<0.05$), HB of after infection (OR: 1.127, $p<0.05$), PLT of after infection (OR: 1.003, $p<0.05$), PTT of during (OR: 0.980, $p<0.05$) and after infections (OR:0.980, $P<0.05$), HSI index of during (OR:0.972, $p<0.05$) and after infections (OR: 0.870, $p<0.05$) as well as AST/ALT ratio of after infection (OR:1.855, $p<0.05$).

Table 4 shows the predictors factors associated with MAFLD in COVID-19 patients in a multivariate logistic regression interpretation. Age, sex and BMI were included as primary covariates in the model to adjust for their known influence on both metabolic dysfunction and COVID-19 severity. The resulting Adjusted OR (adjOR) and 95% Confidence Intervals (CI) therefore represent the independent association of the studied variables with the clinical outcomes, after controlling for these demographic and anthropometric baseline differences shows the predictors factors associated with MAFLD in COVID-19 patients revealed the predictors in this study such as nationality of Saudi (adjOR = 0.289, 95% CI = 0.097 - 0.866, p = 0.027), hospital admission (adjOR = 8.315, 95% CI = 2.642 - 26.175, p = <0.001), COVID-19 Severity (adjOR = 0.291. 95% CI = 0.113 - 0.748, p = 0.010), PLT of after COVID-19 infection (adjOR = 1.003, 95% CI = 1.00 - 1.006, p = 0.028) and AST/ALT ratio of after COVID-19 infection (adjOR = 2.674, 95% CI = 1.183 - 6.044, p = 0.018).

Table 4

Multiple logistic regression analysis on predicting factors associated with MAFLD in COVID-19 patients

Predictors	[a]B	S.E.	Wald	P-value	[d]OR	95% CI	
						Lower	Upper
Age	0.012	0.015	0.686	0.408	1.012	0.984	1.042
Gender							
Male	0.247	0.427	0.336	0.562	1.281	0.555	2.956
Female					Ref		
Nationality							
Saudi	-1.241	0.56	4.912	0.027*	0.289	0.097	0.866
Non-Saudi					Ref		
Presence of comorbidity disease							
Yes	0.334	0.623	0.288	0.592	1.397	0.412	4.737
No					Ref		
Hospital Admission							
Admitted					Ref		
Home isolation	2.118	0.585	13.106	<0.001*	8.315	2.642	26.175
COVID-19 Severity							
Severe	-1.234	0.481	6.578	0.010*	0.291	0.113	0.748
Mild/moderate					Ref		
TBIL *After COVID-19 infection*	-0.002	0.008	0.076	0.783	0.998	0.981	1.014
TP *During COVID-19 infection*	-0.042	0.024	3.074	0.080	0.959	0.916	1.005
HB *After COVID-19 infection*	0.019	0.106	0.032	0.858	1.019	0.828	1.254
RBC *After COVID-19 infection*	0.127	0.127	1.001	0.317	1.135	0.885	1.456
PLT *After COVID-19 infection*	0.003	0.001	4.803	0.028*	1.003	1.000	1.006
APRI *After COVID-19 infection*	-0.138	0.159	0.755	0.385	0.871	0.637	1.190
AST/ALT Ratio *During COVID-19 infection*	0.324	0.290	1.251	0.263	1.383	0.784	2.441
AST/ALT Ratio *After COVID-19 infection*	0.984	0.416	5.592	0.018*	2.674	1.183	6.044

*Note: [a]B; adjusted coefficient, [c]SE: Standard Error; [d]OR: Adjusted Odds ratio, 95% CI: Confidence interval, *p<0.05. Hosmer-Lemeshow test p=0.358, Nagelkerke R^2=0.459.*

DISCUSSION

The findings of this retrospective case-control study reinforce the growing evidence that metabolic dysfunction-associated fatty liver disease (MAFLD) is an important determinant of COVID-19 severity, while also highlighting several observations that differ from previous reports. Most participants were Saudi nationals (71% of controls and 89% of cases), reflecting the study population and limiting the generalizability of the findings to other ethnic groups. Although gender distribution was not significantly different between groups (p = 0.059), contrary to earlier reports suggesting a male predominance in MAFLD (Feng et al., 2020), this discrepancy may be attributed to population-specific

characteristics, lifestyle factors, or sample size. Likewise, age did not differ significantly between groups ($p = 0.131$), despite patients with MAFLD being slightly older (median 55 years) than those without MAFLD (50 years), contrasting with previous studies that identified advancing age as an independent risk factor (Hartl et al., 2022). In contrast, body mass index (BMI) was significantly higher among patients with MAFLD, consistent with the established relationship between obesity, hepatic steatosis, and severe COVID-19 outcomes (Dongiovanni et al., 2020; Ahmad et al., 2021; Malik et al., 2021; Cai et al., 2021). Obesity likely exacerbates systemic inflammation and metabolic dysfunction, thereby increasing the risk of intensive care admission and adverse clinical outcomes. Although both groups exhibited a high prevalence of comorbidities (83% in cases and 88% in controls), no significant between-group difference was observed, differing from previous reports (Tchang et al., 2021). Nevertheless, logistic regression demonstrated that the presence of comorbidities independently predicted MAFLD (adjusted OR = 11.340, 95% CI: 2.190–58.706, $p < 0.05$), supporting evidence that multiple metabolic disorders accelerate disease progression and worsen prognosis (Liu et al., 2022). Clinically, patients with MAFLD experienced significantly poorer outcomes than controls. Severe COVID-19 occurred more frequently among MAFLD patients (61%, $p = 0.031$), hospitalisation rates were markedly higher (43% versus 8%), and mortality was significantly increased, with 31% of deceased patients having MAFLD which aligned with previous study of Bahardoust et al. (2021). These findings support previous studies demonstrating that pre-existing fatty liver disease substantially increases vulnerability to severe SARS-CoV-2 infection, prolonged hospitalisation, and death (Alwafi et al., 2021; Miele et al., 2021; Jagirdhar et al., 2023; Vancsa et al., 2020), although the higher proportion of MAFLD patients managed outside the hospital may also reflect selection bias toward less severe disease. Laboratory findings further emphasize the hepatic involvement associated with COVID-19. Among liver function parameters, only aspartate aminotransferase (AST) showed significant elevation in MAFLD patients ($p < 0.05$), corroborating reports that AST is a sensitive marker of hepatic injury and disease severity in COVID-19 (Radonjić et al., 2022; Huang et al., 2020), whereas mild elevations of liver enzymes have also been reported in patients without underlying liver disease (Zarifian et al., 2020). Significant changes in platelet counts after infection were observed exclusively in MAFLD cases, possibly reflecting anticoagulant therapy administered during hospitalisation, while partial thromboplastin time (PTT) differed significantly between infection and recovery phases, supporting previous evidence of COVID-19-associated blood coagulopathy (Iba et al., 2020; Sarkar et al., 2021; Hanff et al., 2020). In contrast, D-dimer and ferritin did not differ significantly, despite their established association with severe COVID-19 in other studies (Salazar et al., 2021; Del Nonno et al., 2021), a discrepancy that may be explained by incomplete laboratory data and limited sample size. C-reactive protein (CRP), however, remained significantly elevated in critically ill patients, confirming its role as an inflammatory marker of severe infection (Emsen et al., 2022). Beyond conventional laboratory parameters, this study highlights the clinical utility of non-invasive biomarkers for MAFLD. The Hepatic Steatosis Index (HSI) demonstrated significant differences between infection and post-infection periods ($p < 0.05$), supporting recent evidence that HSI is a reliable and practical tool for identifying hepatic steatosis without liver biopsy (Mahamid et al., 2021; Priego-Parra et al., 2024). Similarly, the AST/ALT ratio differed significantly between cases and controls and remained an independent predictor of MAFLD in multivariable logistic regression (adjusted OR = 0.005, 95% CI: 0.001–0.191, $p < 0.05$). Although previous studies have questioned the value of the AST/ALT ratio, particularly in early-stage disease where aminotransferase abnormalities may be minimal (Hernandez & Mohammad, 2020), the present findings suggest that it retains predictive value within this clinical context. BMI also independently predicted MAFLD (adjusted OR = 1.375, 95% CI: 1.066–1.774, $p < 0.05$), reinforcing obesity as a central driver of hepatic steatosis and metabolic dysfunction (Calapod et al., 2020). Collectively, these results indicate that obesity, metabolic comorbidities, HSI, and the AST/ALT ratio represent valuable predictors of MAFLD among patients with COVID-19 and support the increasing role of non-invasive diagnostic approaches for early risk stratification and disease monitoring. Overall, this study demonstrates that patients with concurrent MAFLD and COVID-19 experience substantially poorer clinical outcomes, with an estimated 1.46-fold greater likelihood of mortality-related complications and a 1.22-fold increased risk of severe disease compared with individuals without MAFLD (Vázquez et al., 2022). Although these findings differ from studies reporting no significant effect of MAFLD on mortality (Singh et al., 2021) and from the greater disease severity reported by Ji et al. (2020), such inconsistencies reflect differences in patient demographics, healthcare systems, circulating SARS-CoV-2 variants, and study design. Taken together, the present findings underscore the importance of recognising MAFLD as a clinically relevant metabolic disorder that amplifies COVID-19 severity and support early identification of high-risk individuals through simple, non-invasive biomarkers to facilitate timely intervention and improve patient outcomes.

The PTT measures the time required for clot formation following the activation of the intrinsic coagulation pathways (involving factors XII, XI, IX and VIII), reflecting both clotting function and indirectly the liver function (Zaidi et al., 2025). In COVID-19 patients, a paradoxically shortened PTT is often observed, suggesting a hypercoagulable state. PTT is decreased by high factor VIII levels. Whereby, this can mask underlying coagulation dysfunction in early stages. Moreover, current study suggest that the AST and CRP levels exhibit the increase of inflammation during the severity of COVID-19 in MAFLD patients underscore the infections might trigger the “cytokine storm syndroms” indirectly would affect the PTT. However, increased CRP can lead to disseminated intravascular coagulation (DIC), which can lengthen the PTT due to factor VIII consumption. It is suggested the findings show PTT was longer in cases group (median 36.60 sec) compared to controls (median 34.00 sec) after infection and the CRP and AST levels were elevated. Whereby, AST-predominant signals liver damage led to acute steatohepatitis or sepsis (Xu et. al 2025). It has been shown that the

MAFLD may be associated with worsened outcomes which leads to multiorgan failure and dysregulated released of pro-inflammatory cytokines (Cordeiro et al., 2022). The inverse association between severity and recovery (OR = 0.535) is clinically intuitive; it demonstrates that higher baseline physiological stress compounded by MAFLD significantly diminishes the probability of a favourable clinical trajectory. Every unit increase in the severity scale effectively halves the likelihood of recovery within the observed timeframe. While hospital admission usually indicates a more severe case, the OR of 9.4 in our model suggests that hospitalized patients had significantly higher odds of documented recovery. This likely reflects the intensive medical intervention and standardized discharge protocols received in-hospital, which facilitated recovery compared to the unmonitored home-isolation group. While our model clearly identifies clinical severity as a barrier to recovery (OR = 0.535), the relationship between initial severity and ultimate mortality in the MAFLD cohort was less linear than initially hypothesized. This observation may be partially explained by the aggressive clinical management of high-severity cases, which may have mitigated the expected mortality rate. Consequently, while severity remains a critical prognostic marker, its role as a definitive predictor of mortality requires further validation in larger, multi-center cohorts.

Furthermore, the comprehensive analysis identified obesity, and HSI index are the predictors of MAFLD as well. The ALT/AST ratio of less than 1 also is similar with previous study (Chen et al., 2021). Notably, in a retrospective study of 585 subjects, HSI was strongly validated as a diagnostic tool for MAFLD (Priego-Parra et al., 2024). Importantly, HSI, when combined with COVID-19 infection status, proved to be a robust non-invasive prognostic indicator for MAFLD patients, reducing reliance on radiographic procedures. Interestingly, our data indicated a higher incidence of severe COVID-19 in the control group compared to the MAFLD cohort. This apparent paradox is attributable to the higher prevalence of non-metabolic comorbidities within the control arm (52% vs. 48% in the MAFLD group). In clinical practice, patients without MAFLD who require hospitalization for COVID-19 often present with other high-risk conditions that independently drive disease severity. Therefore, the observed severity rates reflect the cumulative physiological stress of these baseline comorbidities, which outweighed the specific impact of MAFLD in this particular study population. Contrary to previous studies, our data showed MAFLD patients were more likely to be managed at home (64% vs 36%) and had lower rates of severe COVID-19 (61% vs 75% in non-MAFLD). This may reflect selection bias, younger age of MAFLD patients, or differences in healthcare-seeking behaviour. In our cohort, MAFLD patients had a mortality rate of 31.3% (35/112), while no non-MAFLD patients died.

There are limitations due to its retrospective and case-control design, as well as inadequate data in specific patient records linked to the increased workload of healthcare professionals during the pandemic. The severity of COVID-19 has a strong correlation with MAFLD, obesity, hypertension, and metabolic syndrome. The present study further explains the potential influence of these biomarkers on clinical practice. Initially, those biomarkers can detect hepatic steatosis in retrospective series when ultrasonography is unavailable. Hepatic ultrasonography is not frequently utilized in metabolic assessment, although being highly recommended. From a hepatic point of view, the evaluation of steatosis lacks clinical relevance since the quantity of fat in the liver does not consistently reflect the progression of liver disease. While the control group in this study exhibited a 0% mortality rate, this should be interpreted within the context of their favorable baseline metabolic health. The rigorous exclusion of MAFLD-related criteria in the control arm likely isolated a population with high physiological reserve. It was acknowledged that the lack of mortality in this group may reflect the specific sample size and local demographic profile; however, the standardized and concurrent recruitment of both cases and controls mitigates the risk of systematic selection bias. Further investigation through substantial prospective studies is needed to comprehensively understand the impact of MAFLD and metabolic syndrome on the progression of severe COVID-19.

CONCLUSION

Our study identifies a significant association between MAFLD and a prolonged clinical course in patients with COVID-19. Within this retrospective cohort, the presence of metabolic dysfunction served as a statistically significant predictor of increased disease severity and reduced odds of recovery (OR = 0.535). These findings suggest that MAFLD status may be linked to a more complex clinical trajectory, although the retrospective nature of this study necessitates prospective research to further elucidate the underlying mechanisms.

The global impact of SARS-CoV-2 has highlighted the clinical vulnerability of individuals with chronic liver conditions. Our analysis revealed significant correlations between COVID-19 progression and pre-existing MAFLD, alongside key covariates including BMI, nationality, and hospital admission status. Furthermore, specific biochemical parameters including TBIL, HB, and PTT demonstrated distinct patterns following infection. Notably, nationality, clinical severity, and the post-infection AST/ALT ratio were identified as prognostic markers suggesting that a pre-existing MAFLD profile may be associated with a more severe COVID-19 course.

Consequently, in this study population, patients with MAFLD demonstrated a higher frequency of severe complications compared to those without the condition. While a trend toward increased mortality was observed in the MAFLD cohort, we acknowledge that baseline comorbidity imbalances in the control group may have influenced these proportions. These results underscore the clinical importance of monitoring MAFLD as a potential risk-stratification tool to assist in the management of adverse outcomes.

AUTHOR CONTRIBUTIONS

The study was conducted by Mesk Saleh Ali Ghulais under the supervision of Hasni Idayu Saidi and Nurliyana Najwa Md Razip. Mesk Saleh Ali Ghulais, Nurliyana Najwa Md Razip, and AbdulRahman Muthanna contributed equally to the manuscript preparation and formal analysis. Hasni Idayu Saidi and Nurliyana Najwa Md Razip contributed to the conceptualization, supervision, and validation of the study. Huzwah Khazai, Khaled Belal, and Ummi Nadira Daut also contributed equally to the supervision and validation of the study.

ETHICS APPROVAL

The study protocol was approved by the Ethics and Research Committee of King Fahad Hospital Hofuf, Al Ahsa Kingdom of Saudi Arabia, with approval reference IRB-KFHH Number (H-05-HS-065) 13-09-2021/KFHH-RCA No:32-43-2021 with declaration of Helsinki guideline.

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Not applicable.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest in the work.

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