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Original article

Study on the Impact of Metabolic Associated Fatty Liver Disease (MAFLD) on Patients with Corona Virus Disease – 2019 (COVID-19)

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Abstract

Purpose: This study's purpose was to assess the impact of metabolic associated fatty liver disease (MAFLD) on the outcome of patients affected by Corona Virus Disease – 2019 (COVID-19). ***Patients and Methods:*** This prospective observational study `was conducted on patients affected by COVID-19 who were treated at our Hospital from January 2022 to February 2023. The study involved 200 adult patients with confirmed COVID-19, excluding those with other chronic hepatic disorders, and included comprehensive clinical, laboratory, and ultrasonographic assessments. The existence of MAFLD was assessed as newly established, and the COVID-19 severity was evaluated per the Egyptian protocol, and the diagnosis of MAFLD followed international consensus criteria. ***Results:*** Patients with MAFLD and COVID-19 (Group I) had a significantly higher number of patients with severe disease (n = 60, 60%) than patients with COVID-19 alone (Group II) (n = 21, 21%, p < 0.001). The mortality rate was 11% (n = 22), with a significantly higher rate encountered in Group I (n = 16, 16% vs. n = 6, 6%, p = 0.024). ***Conclusion:*** Patients with MAFLD exhibited distinct clinical and laboratory features and were more likely to develop severe COVID-19, with a higher mortality rate.

Key words: COVID-19, metabolic associated fatty liver disease (MAFLD), outcome.

Introduction

The global impact of Corona Virus Disease – 2019 (COVID-19), a disease developed by infection with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV2), has touched the lives of countless individuals. This outbreak initially surfaced in China, towards the conclusion of 2019 [(1)]. Subsequently, it rapidly disseminated across the world, with documented cases in over 180 nations. This compelled the World Health Organization (WHO) to endorse it as a pandemic in February 2020, a designation it maintains as it continues to cause the loss of thousands of lives daily [(2)].

In the initial stages of the pandemic, it became evident that although COVID-19 primarily manifests with respiratory symptoms, it exerts its influence on a range of organ systems, including the cardiovascular, hematological, neurological, gastrointestinal, and renal systems [(3-6)].

Liver damage stands out as a significant aspect of COVID-19, as it is associated with elevated hepatic enzymes in up to 65% of patients during the acute state (7, 8), and some individuals experience post-COVID-19 hepatic complications (9, 10). Various factors contribute to this liver damage, including direct viral hepatic cytotoxicity, hypoxic effects, the systemic inflammatory process, coagulopathic changes, and drug-induced liver toxicity [(5)].

Notably, angiotensin-converting enzyme 2 (ACE2) is a main entry route for SARS-COV-2, and it is intriguing to observe that inflammatory processes and hypoxic states can up regulate ACE-2 expression (11, 12). It's important to mention that patients with pre-existing chronic liver diseases may experience more severe liver injury, partly due to the elevated ACE2 expression in these individuals [(12–14)].

Non-alcoholic fatty liver disease (NAFLD) is a globally prevalent disorder. Recognizing that the term "NAFLD" does not adequately manifest our stream understanding of the condition, a panel of experts has proposed a more fitting terminology: metabolically associated fatty liver disease, or "MAFLD." According to an experts provided international consensus, MAFLD is characterized by the existence of liver steatosis in individuals who meet a minimum of being overweight or obese, showing indication of metabolic dysfunction, or having type 2 diabetes mellitus (DM) [(15, 16)].

MAFLD has been associated with the risk of experiencing more severe infections, including conditions like community-acquired pneumonia and other infectious diseases [(17)]. Nevertheless, it remains a subject of debate whether MAFLD is implicated in advancing the progression of COVID-19 infection. Therefore, this study aimed to evaluate the impact of MAFLD on patients affected by COVID-19, and the potential predictors of COVID-19-associated mortality.

Patients and methods

This is a prospective observational study that involved patients affected by COVID-19 who were managed in Toukh Fever hospital during the period from January

2022 to February 2023. The study was conducted after approval by the Research Ethics Committee (No. 2-2022/12), and the Declaration of Helsinki was adhered to.

All adult patients who were presented to the hospital with COVID-19 were eligible for the study if the infection was proved using the polymerase chain reaction (PCR). Patients with a history of alcohol intake, chronic viral hepatitis, autoimmune hepatitis, systemic debilitating disease, or malignancy were excluded. Patients were followed-up until their discharge from hospital, either with recovery or mortality. Patients with incomplete required data were also excluded. A written informed consent was obtained from each included patient.

The study patients (n = 200) underwent detailed history-taking and a full clinical examination. A comprehensive battery of laboratory tests was conducted to evaluate various aspects of the patients' health. These tests encompassed assessments of hemoglobin (Hb) levels (in g/dL), total leukocyte count (TLC) × 10^9 cells/L, lymphocyte counts × 10^9 cells/L, platelet count × 10^9 cells/L, serum creatinine levels (in mg/dL), C-reactive protein (CRP) levels (in mg/L), ferritin levels (in ng/mL), lipid profile (in mg/dL), D-dimer (in µg/L), aspartate aminotransferase (AST) levels (in U/L), and alanine aminotransferase (ALT) levels (in U/L).

All patients were subjected to ultrasonographic examinations that were performed by an expert radiologist who was blinded to the clinical and laboratory conditions. The examination was done using a Mindray 2200 Medica apparatus equipped with a probe suitable for abdominal examination (3–5 MHz probe). The degree of liver steatosis was assessed using a semi-quantitative scoring system on a scale of 0 to 3, where 0 indicated the absence of steatosis, 1 denoted mild steatosis, 2 signified moderate steatosis, and 3 represented severe steatosis. This grading of steatosis followed the criteria established by Saverymuttu et al. [(18)], which took into consideration the presence of abnormal high-level echoes emanating from the parenchyma of the liver, the discrepancy in the amplitude of echo between the hepatic and renal parenchyma, the extent of penetration of echo into the deeper sections of the liver, and the ability to delineate the structure of the hepatic blood vessels.

The severity of COVID was determined per Egyptian protocol for diagnosis and treatment version 1.4 [(19)], in which severe cases were defined as those with any of the following criteria: respiratory rate > 30, oxygen saturation < 92 at room air, the partial pressure of oxygen (PaO2) by the fraction of inspired oxygen (FiO2)o < 300, and /or chest radiology showing more than 50% lesion or progressive lesion within 24 to 48 hours. The MAFLD diagnosis was done per the novel proposed criteria [(15, 16)], which defined patient as having MAFLD if there was evidence of hepatic steatosis (mostly by imaging) with at least one of the following metabolic abnormalities: overweight/obesity, type 2 diabetes mellitus, and/or two or more signs of metabolic dysregulation that included hypertension, dyslipidemia, prediabetes, insulin resistance, and elevated CRP.

The study patients with COVID-19 were categorized into Group I, which included

patients with MAFLD, and Group II, which included patients without MAFLD.

The statistical analytic processes were implemented using IBM SPSS Statistics version 27 (IBM Inc., Armonk, NY, USA). For comparison of the numerical and categorical data, the independent t test and the chi-square test were used, respectively. To assess the predictors for COVID-19-associated mortality, binary logistic regression analysis was performed with a calculation of the odds ratios (ORs) and their confidence intervals (CIs). The differences between groups were judged as statistically significant if p-values were less than 0.05.

Results

This study involved a total of 100 patients in each group. The patients' ages ranged from 47 to 72 years, with a mean of 59.99 ± 6.77 in Group I and 60.46 ± 7.07 in Group II. Males comprised more than half of the study patients, constituting 57% of Group I (n = 57) and 60% of Group II (n = 60). Both groups had comparable mean age (p = 0.632) and the sex distribution (p = 0.677).

The patients body mass index (BMI; kg/m^2) was higher in Group I (27.52 ± 1.51) than Group II (25.5 ± 1.26), with a statistically significant difference (p < 0.001). Smoking prevalence was rather similar in the two groups (13% in Group I and 16% in Group II, p = 0.547). Patients in Group I had a significantly higher prevalence of hypertension (48% vs. 29%, p = 0.009) and type 2 DM (34% vs. 11%, p < 0.001) (Table 1).

Concerning the laboratory findings, patients in Group I exhibited significantly lower hemoglobin levels (11.04 ± 0.9 vs. 11.57 ± 0.6, p < 0.001), lymphocyte counts (0.709 ± 0.17 vs. 0.871 ± 0.35, p < 0.001), and HDL levels (59.6 ± 14.9 vs. 79.7 ± 13.5, p < 0.001). Platelet counts were comparable (239.18 ± 71.16 vs. 251.97 ± 45, p = 0.131). Group I also showed significantly higher TLC (8.72 ± 3.9 vs. 7.38 ± 3.6, p = 0.014), CRP levels (70.45 ± 26.1 vs. 58.79 ± 32.3, p = 0.005), ferritin levels (468.9 ± 190.7 vs. 357.3 ± 189, p < 0.001), creatinine levels (1.23 ± 0.33 vs. 1.04 ± 0.35, p < 0.001), D-dimer (599.96 ± 226.99 vs. 442.37 ± 227.55, p < 0.001), ALT levels (80.56 ± 31.7 vs. 64.37 ± 29.5, p < 0.001), AST levels (61.8 ± 24.6 vs. 50.86 ± 26.3, p = 0.001), LDL levels (136.1 ± 39.3 vs. 75 ± 23.1, p < 0.001), TG levels (271.23 ± 85.3 vs. 192.28 ± 47, p < 0.001) (Table 2).

The ultrasound assessment revealed that grade 1, grade 2, and grade 3 steatosis were found in 18% (n = 18), 52% (n = 52), and 30% (n = 30) of the patients in Group I, respectively, while all patients in Group II (100%) had grade 0 steatosis (p<0.001) (Table 3).

As for disease severity, Group I showed a significantly higher number of patients with severe disease (n = 60, 60%) than Group II (n = 21, 21%) (p < 0.001). The mortality rate was 11% (n = 22), with a significantly higher rate encountered in Group I (n = 16, 16% vs. n = 6, 6%, p = 0.024) (Table 4, Figure 1, 2).

Binary logistic regression revealed that the predictors of mortality in all patients affected by COVID-19 were the presence of MAFLD (OR = 2.98, CI = 1.12 – 7.98,

p = 0.029), BMI (OR = 1.36, CI = 1.04 – 1.98, p = 0.024), lymphocytes count (OR = 0.036, CI = 0.003 – 0.377, p = 0.006), CRP (OR = 1.022, CI = 1.005 – 1.04, p = 0.013), AST (OR = 1.024, CI = 1.004 – 1.044, p = 0.018), ALT (OR = 1.022, CI = 1.007 – 1.037, p = 0.005), LDL (OR = 1.011, CI = 1.002 – 1.021, p = 0.021), HDL (OR = 0.955, CI = 0.927 – 0.983, p = 0.002), ferritin (OR = 1.003, CI = 1.0 – 1.005, p = 0.021), D-dimer (OR = 1.002, CI = 1.0 – 1.004, p = 0.025), and the classification as a severe disease (OR = 0.165, CI = 0.058 – 0.469, p < 0.001) (Table 5).

Table 1: The patients demographic characteristics

Characteristic	Group I	Group II	p-value
Age (years): mean ± SD	59.99 ± 6.77	60.46 ± 7.07	0.632
Male Sex: n (%)	57 (57%)	60 (60%)	0.677
BMI (kg/m2): mean ± SD	27.52 ± 1.51	25.5 ± 1.26	<0.001*
Smoking: n (%)	13 (13%)	16 (16%)	0.547
Hypertension: n (%)	48 (48%)	29 (29%)	0.009*
Type 2 diabetes mellitus: n (%)	34 (34%)	11 (11%)	<0.001*

BMI: body mass index, *: statistically significant.

Table 2: The patients' laboratory findings

Laboratory Parameter	Group I mean ± SD	Group II mean ± SD	p-value
Hemoglobin (g/dL)	11.04 ± 0.9	11.57 ± 0.6	<0.001*
Lymphocyte Count (× 10^9 cells/L)	0.709 ± 0.17	0.871 ± 0.35	<0.001*
HDL Levels (mg/dL)	59.6 ± 14.9	79.7 ± 13.5	<0.001*
Platelet Count (× 10^9 cells/L)	239.18 ± 71.16	251.97 ± 45	0.131
TLC (× 10^9 cells/L)	8.72 ± 3.9	7.38 ± 3.6	0.014*
CRP Levels (mg/L)	70.45 ± 26.1	58.79 ± 32.3	0.005*
Ferritin Levels (ng/mL)	468.9 ± 190.7	357.3 ± 189	<0.001*
Creatinine Levels (mg/dL)	1.23 ± 0.33	1.04 ± 0.35	<0.001*
ALT Levels (U/L)	80.56 ± 31.7	64.37 ± 29.5	<0.001*
AST Levels (U/L)	61.8 ± 24.6	50.86 ± 26.3	0.001*
LDL Levels (mg/dL)	136.1 ± 39.3	75 ± 23.1	<0.001*
TG Levels (mg/dL)	271.23 ± 85.3	192.28 ± 47	<0.001*

MAFLD: Metabolic Associated Fatty Liver Disease, BMI: Body Mass Index, CRP: C-Reactive Protein, AST: Aspartate Aminotransferase, ALT: Alanine Aminotransferase, LDL: Low-Density Lipoprotein, HDL: High-Density Lipoprotein, *: statistically significant.

Table 3: The patients' ultrasound hepatic steatosis grade

Steatosis Grade	Group I	Group II	p-value
Grade 0 (None)	0 (0%)	100 (100%)	<0.001*
Grade 1 (Mild)	18 (18%)	0 (0%)	
Grade 2 (Moderate)	52 (52%)	0 (0%)	
Grade 3 (Severe)	30 (30%)	0 (0%)	

Table 4: Disease severity and mortality

	Group I	Group II	p-value
Mild COVID-19: n (%)	15 (15%)	50 (50%)	<0.001*
Moderate COVID-19: n (%)	25 (25%)	29 (29%)	
Severe COVID-19: n (%)	60 (60%)	21 (21%)	
Mortality: n (%)	16 (16%)	6 (6%)	0.024*

Table 5: Predictors of mortality in the study patients:

Predictor	Odds Ratio	95% CI	p-value
MAFLD	**2.98**	**1.12 – 7.98**	**0.029**
BMI	**1.36**	**1.04 – 1.98**	**0.024**
Lymphocytes Count	**0.036**	**0.003 – 0.377**	**0.006**
CRP	**1.022**	**1.005 – 1.04**	**0.013**
AST	**1.024**	**1.004 – 1.044**	**0.018**
ALT	**1.022**	**1.007 – 1.037**	**0.005**
LDL	**1.011**	**1.002 – 1.021**	**0.021**
HDL	**0.955**	**0.927 – 0.983**	**0.002**
Ferritin	**1.003**	**1.0 – 1.005**	**0.021**
D-dimer	**1.002**	**1.0 – 1.004**	**0.025**
Severe Disease	**0.165**	**0.058 – 0.469**	**< 0.001**

MAFLD: Metabolic Associated Fatty Liver Disease, BMI: Body Mass Index, CRP: C-Reactive Protein, AST: Aspartate Aminotransferase, ALT: Alanine Aminotransferase, LDL: Low-Density Lipoprotein, HDL: High-Density Lipoprotein, CI: Confidence Interval*: statistically significant.

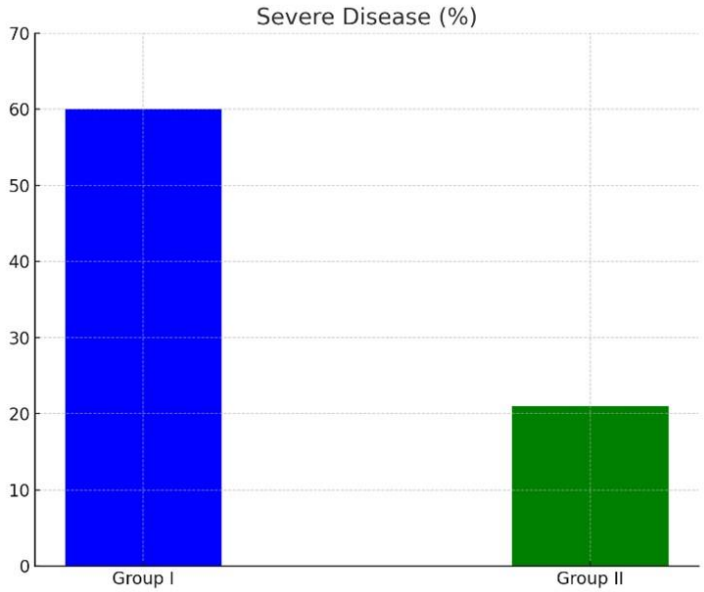

Figure 1: The percentage of severe disease in both groups.

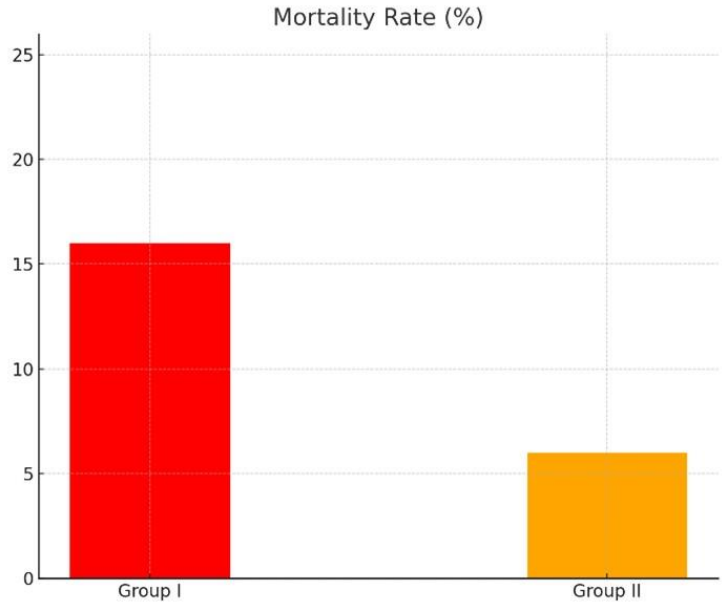

Figure 2: The percentage of mortality in both groups.

Discussion

In light of the ongoing global pandemic, understanding the relationship between pre-existing metabolic conditions such as MAFLD and COVID-19 severity is of paramount importance.

In this study, patients with MAFLD were found to have a significantly higher BMI compared to those without MAFLD. This finding is consistent with previous research indicating that obesity is a predisposing factor for both MAFLD [(20)] and severe COVID-19 [(21)]. Furthermore, patients with MAFLD had a higher prevalence of hypertension and type 2 diabetes mellitus (DM). Both hypertension and type 2 DM are common comorbidities in individuals with MAFLD [(22)]. It is known that these conditions can exacerbate the severity of COVID-19 [(23)]. Therefore, the presence of MAFLD, along with its associated comorbidities, may increase the odds of developing severe COVID-19.

The observed lower hemoglobin levels in patients with MAFLD raise concerns about the presence of anemia. Anemia has been recognized as a potential predisposing factor for developing severe COVID-19, as it can exacerbate hypoxia and weaken the body's immune response [(24)]. Lymphocyte counts, a critical component of the immune system, were significantly lower in patients with MAFLD. Reduced lymphocyte counts are associated with immune system dysfunction and have been linked to severe COVID-19 [(25)]. These findings suggest that patients with MAFLD may face additional challenges in mounting an effective immune response against the virus, which could contribute to worse outcomes.

Elevated TLC, CRP, and ferritin in patients with MAFLD suggest a more robust inflammatory response in this group. These are hallmarks of the cytokine storm, a severe immunogenic response seen in some COVID-19 cases that can

lead to tissue damage and multi-organ failure [26]. The finding emphasizes the need for vigilant monitoring and tailored therapeutic interventions in COVID-19 patients with MAFLD to mitigate the potential consequences of an exaggerated immune response.

The reduced levels of HDL and the higher levels of LDL and triglycerides in patients with MAFLD are denoting dyslipidemia that can heighten cardiovascular risk [27], which is particularly relevant in the context of both MAFLD and COVID-19, as these conditions have well-documented impacts on the cardiovascular system [28].

Another notable finding is the higher creatinine levels in patients with MAFLD, indicating potential kidney dysfunction. Kidney injury is a recognized sequel of severe COVID-19 [6], and the coexistence of MAFLD may exacerbate these complications.

The significantly elevated levels of ALT and AST in patients with MAFLD underscore the impact of pre-existing liver conditions on the liver's response to COVID-19. These findings align with the concept that MAFLD primarily affects the liver and that the liver's capacity to cope with additional stress from viral infections may be compromised [22].

In this study, we observed a noteworthy elevation in the D-dimer levels in patients with MAFLD who were affected by COVID-19. This observation has important clinical implications. Elevated D-dimer levels often indicate an increased risk of thrombosis or blood clot formation [26]. In the context of COVID-19, with the established elevated risk of clotting disorders [3,10], the findings suggest that MAFLD patients with COVID-19 may face a heightened risk of clot-related complications and the susceptibility to severe forms of the disease.

In congruence with this work, the recent study of Milivojević et al. [29] found that patients with MAFLD and COVID-19, when compared to those with COVID-19 only, had significantly higher BMI measures, diabetes mellitus, and hypertension prevalence, as well as a worse lipid profile and higher CRP, ferritin, and D-dimer. Also, the study of Vrsaljko et al. [30] demonstrated significantly higher levels of AST, ALT, and inflammatory biomarkers in patients with MAFLD and COVID-19 than those with COVID-19 only.

Regarding disease severity, patients having MAFLD were more likely to develop severe COVID-19, and the mortality rate was also higher among this group. These results are supported by previous studies linking MAFLD to the worse outcome of COVID-19 [29, 30]. As for mortality, Milivojević et al. [29], in line with this study, found that the presence of MAFLD was a significant predictor for mortality in patients with COVID-19. Moreover, the study of Lopez-Mendez et al. [36] identified heightened risks of mortality associated with MAFLD in patients with COVID-19. Additionally, analyses done by Kim et al. [37] based on the United States national mortality records showed that the previously consistent rise in MAFLD-associated mortality accelerated during the COVID-19 pandemic.

Given that metabolic elements like obesity and diabetes are well-recognized to be

associated with severe cases of COVID-19 and predispose to high risk of mortality [31], it is reasonable to infer that a poorer prognosis for COVID-19 is also linked to MAFLD [32]. The reasons behind these unfavorable outcomes have sparked debate, with various potential mechanisms coming into play. Some argue that, in patients affected by COVID-19, MAFLD may exaggerate the cytokine storm seen by triggering the liver to produce pro-inflammatory cytokines [33, 34]. Conversely, an alternative hypothesis posits that natural immunity weakens as the immune cells transition in the liver from pro-inflammatory macrophages (M1) to regulatory macrophages (M2) [35], potentially contributing to the worsening of a patient's condition. Another plausible mechanism could be the ACE2 upregulation in patients with MAFLD [33]. These mechanisms collectively contribute to the unfavorable prognosis of the disease, leading to more severe cases and an increased mortality rate.

While this study provides valuable insights, it is not without limitations. The research was performed at a single center, which might limit this study findings generalizability. Additionally, the study design is observational, which cannot establish causal relationships.

Conclusion

This work demonstrated that MAFLD was associated with poorer outcomes in patients affected by COVID-19, including a significantly higher cases developing severe disease and mortality cases. These findings emphasize the need for increased vigilance and monitoring of patients with MAFLD when they contract COVID-19. Moreover, future research should explore the mechanistic links between MAFLD, metabolic dysfunction, and the immune response to COVID-19, as a better understanding of these connections may lead to improved therapeutic strategies.

References

1. Report of the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-19) [Internet]. Available from: https://www.who.int/publications-detail-redirect/report-of-the-who-china-joint-mission-on-coronavirus-disease-2019-(covid-19).

2. WHO Coronavirus (COVID-19) Dashboard. Available from: WHO Coronavirus (COVID-19) Dashboard | WHO Coronavirus (COVID-19) Dashboard With Vaccination Data

3. Momtazmanesh S, Shobeiri P, Hanaei S, Mahmoud-Elsayed H, Dalvi B, Malakan Rad E. Cardiovascular disease in COVID-19: a systematic review and meta-analysis of 10,898 patients and proposal of a triage risk stratification tool. Egypt Heart J. 2020 Jul 13;72(1):41.

4. Harapan BN, Yoo HJ. Neurological symptoms, manifestations, and complications associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease 19 (COVID-19). J Neurol. 2021 Sep;268(9):3059-3071.

5. Nardo AD, Schneeweiss-Gleixner M, Bakail M, Dixon ED, Lax SF, Trauner M. Pathophysiological mechanisms of liver injury in COVID-19. Liver Int. 2021 Jan;41(1):20-32.

6. Yang X, Tian S, Guo H. Acute kidney injury and renal replacement therapy in COVID-19 patients: A systematic review and meta-analysis. Int Immunopharmacol. 2021 Jan;90:107159.

7. Marjot T, Webb GJ, Barritt AS 4th, Moon AM, Stamataki Z, Wong VW, et al. COVID-19 and liver disease: mechanistic and clinical perspectives. Nat Rev Gastroenterol Hepatol. 2021 May;18(5):348-364.

8. Zhang C, Shi L, Wang FS. Liver injury in COVID-19: management and challenges.

Lancet Gastroenterol Hepatol. 2020 May;5(5):428-430.

9. Roth NC, Kim A, Vitkovski T, Xia J, Ramirez G, Bernstein D, Crawford JM. Post-COVID-19 Cholangiopathy: A Novel Entity. Am J Gastroenterol. 2021 May 1;116(5):1077-1082.

10. Xu Z, Shi L, Wang Y, Zhang J, Huang L, Zhang C, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. Lancet Respir Med. 2020 Apr;8(4):420-422.

11. Paizis G, Tikellis C, Cooper ME, Schembri JM, Lew RA, Smith AI, et al. Chronic liver injury in rats and humans upregulates the novel enzyme angiotensin converting enzyme 2. Gut. 2005 Dec;54(12):1790-6.

12. Suárez-Fariñas M, Tokuyama M, Wei G, Huang R, Livanos A, Jha D, et al. Intestinal Inflammation Modulates the Expression of ACE2 and TMPRSS2 and Potentially Overlaps With the Pathogenesis of SARS-CoV-2-related Disease. Gastroenterology. 2021 Jan;160(1):287-301.e20.

13. Soldo J, Heni M, Königsrainer A, Häring HU, Birkenfeld AL, Peter A. Increased Hepatic ACE2 Expression in NAFL and Diabetes-A Risk for COVID-19 Patients? Diabetes Care. 2020 Oct;43(10):e134-e136.

14. Fondevila MF, Mercado-Gómez M, Rodríguez A, Gonzalez-Rellan MJ, Iruzubieta P, Valentí V, et al. Obese patients with NASH have increased hepatic expression of SARS-CoV-2 critical entry points. J Hepatol. 2021 Feb;74(2):469-471.

15. Eslam M, Newsome PN, Sarin SK, Anstee QM, Targher G, Romero-Gomez M, et al. A new definition for metabolic dysfunction-associated fatty liver disease: An international expert consensus statement. J Hepatol. 2020 Jul;73(1):202-209.

16. Eslam M, Sanyal AJ, George J; International Consensus Panel. MAFLD: A Consensus-Driven Proposed Nomenclature for Metabolic Associated Fatty Liver Disease. Gastroenterology. 2020 May;158(7):1999-2014.e1.

17. Nseir WB, Mograbi JM, Amara AE, Abu Elheja OH, Mahamid MN. Non-alcoholic fatty liver disease and 30-day all-cause mortality in adult patients with community-acquired pneumonia. QJM. 2019; 112:95–99.

18. Saverymuttu SH, Joseph AE, Maxwell JD. Ultrasound scanning in the detection of hepatic fibrosis and steatosis. Br Med J (Clin Res Ed) 1986;292:13–15.

19. Masoud H, Elassal G, Zaky S, Baki A, Ibrahem H, Amin W, et al. Management Protocol for COVID-19 Patients Version 1.4/30th May 2020. Ministry of Health and Population (MOHP), Egypt. 2020.

20. Kaya E, Yilmaz Y. Metabolic-associated Fatty Liver Disease (MAFLD): A Multi-systemic Disease Beyond the Liver. J Clin Transl Hepatol. 2022 Apr 28;10(2):329-338.

21. Singh R, Rathore SS, Khan H, Karale S, Chawla Y, Iqbal K, et al. Association of Obesity With COVID-19 Severity and Mortality: An Updated Systemic Review, Meta-Analysis, and Meta-Regression. Front Endocrinol (Lausanne). 2022 Jun 3;13:780872.

22. Pipitone RM, Ciccioli C, Infantino G, La Mantia C, Parisi S, Tulone A, et al. MAFLD: a multisystem disease. Ther Adv Endocrinol Metab. 2023 Jan 28;14:20420188221145549.

23. de Almeida-Pititto B, Dualib PM, Zajdenverg L. Severity and mortality of COVID-19 in patients with diabetes, hypertension, and cardiovascular disease: a meta-analysis. Diabetol Metab Syndr. 2020;12:75.

24. Bergamaschi G, Borrelli de Andreis F, Aronico N, Lenti MV, Barteselli C, et al; Internal Medicine Covid-19 Collaborators. Anemia in patients with Covid-19: pathogenesis and clinical significance. Clin Exp Med. 2021 May;21(2):239-246.

25. Tavakolpour S, Rakhshandehroo T, Wei EX, Rashidian M. Lymphopenia during the COVID-19 infection: What it shows and what can be learned. Immunol Lett. 2020 Sep;225:31-32.

26. Melo AKG, Milby KM, Caparroz ALMA, Pinto ACPN, Santos RRP, Rocha AP, et al. Biomarkers of cytokine storm as red flags for severe and fatal COVID-19 cases: A living systematic review and meta-analysis. PLoS One. 2021 Jun 29;16(6):e0253894.

27. Hedayatnia M, Asadi Z, Zare-Feyzabadi R, Yaghooti-Khorasani M, Ghazizadeh H, Ghaffarian-Zirak R, et al. Dyslipidemia and cardiovascular disease risk among the MASHAD study population. Lipids Health Dis. 2020 Mar 16;19(1):42.

28. Dongiovanni P, Meroni M, Longo M, Fracanzani AL. MAFLD in COVID-19 patients: an insidious enemy. Expert Rev Gastroenterol Hepatol. 2020;14(10):867-872.

29. Milivojević V, Bogdanović J, Babić I, Todorović N, Ranković I. Metabolic Associated Fatty Liver Disease (MAFLD) and COVID-19 Infection: An Independent Predictor of Poor Disease Outcome? Medicina (Kaunas). 2023 Aug 8;59(8):1438.

30. Vrsaljko N, Samadan L, Viskovic K, Mehmedović A, Budimir J, Vince A, et al. Association of Nonalcoholic Fatty Liver Disease With COVID-19 Severity and Pulmonary Thrombosis: CovidFAT, a Prospective, Observational Cohort Study. Open Forum Infect Dis. 2022 Feb 9;9(4):ofac073.

31. National Institutes of Health. (2023). Clinical Spectrum of SARS-CoV-2 infection. Available at: https://www.covid19treatmentguidelines.nih.gov/overview/clinical-spectrum/

32. Gonzáles Yovera JG, Concepción-Zavaleta MJ, Coronado Arroyo J, Moreno Marreros D. Confluence of obesity and MAFLD during Covid-19 pandemic in a developing country. Endocrinol Diabetes Metab. 2021 Apr;4(2):e00189.

33. Targher G, Mantovani A, Byrne CD, Wang XB, Yan HD, Sun QFet al. Risk of severe illness from COVID-19 in patients with metabolic dysfunction-associated fatty liver disease and increased fibrosis scores. Gut. 2020 Aug;69(8):1545-1547.

34. Sharma P, Kumar A. Metabolic dysfunction associated fatty liver disease increases risk of severe Covid-19. Diabetes Metab Syndr. 2020 Sep-Oct;14(5):825-827.

35. Lefere S, Tacke F. Macrophages in obesity and non-alcoholic fatty liver disease: Crosstalk with metabolism. JHEP Rep. 2019 Feb 23;1(1):30-43.

36. Lopez-Mendez I, Aquino-Matus J, Gall SM, Prieto-Nava JD, Juarez-Hernandez E, Uribe M, Castro-Narro G. Association of liver steatosis and fibrosis with clinical outcomes in patients with SARS-CoV-2 infection (COVID-19). Ann Hepatol. 2021 Jan-Feb;20:100271.

37. Kim D, Alshuwaykh O, Dennis BB, Cholankeril G, Ahmed A. Trends in Etiology-based mortality from chronic liver disease before and during COVID-19 pandemic in the United States. Clin Gastroenterol Hepatol. 2022; 20:2307–2316.e3

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