

How to Cite:

Alhijazien, S. H. S., Aldaoud, S. O. F., Alzayadi, M. T. A., Sarhan, M. R. M. A., Aldomi, M. K. A., & Shawabkeh, T. A. S. A. (2022). Gastrointestinal manifestations in patients with COVID-19 it's correlation with overall clinical outcomes. *International Journal of Health Sciences*, 6(S10), 876-889. <https://doi.org/10.53730/ijhs.v6nS10.13714>

Gastrointestinal manifestations in patients with COVID-19 it's correlation with overall clinical outcomes

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Abstract--Background: The coronavirus disease 2019 (COVID-19) is not just a disease of the respiratory system. The virus can affect the gastrointestinal (GI) tract as well. Recognizing the various manifestations in every organ system is important because these manifestations can contribute to community-based transmission. Aim: The aim of this study is to report the impact of gastrointestinal associated with coronavirus disease (COVID-19). Methods: A retrospective study was conducted in our COVID-19 isolation department at Queen Alia Military Hospital, Royal Medical Services, Amman, Jordan between Mar 2020 and Sep 2021 for all eligible COVID-19 infected hospitalized patients. Because of the retrospective nature of our research, a sign consent form was waived. All admitted COVID-19 infected patients, who were admitted for at least 3 days and whose retrieved data from our electronic medical record system (Hakeem) were available, were grouped into either Higher Liver Disease Status (Status I) and Lower Liver Disease Status (Status II). Higher versus lower liver disease statuses were based on Child-Pugh Score ≥ 8 or < 8 , respectively. An independent T-Tests was used to

analyze the non-parametric and parametric outcomes' data. For non-parametric data, a Chi Square Test was used to analyzed those data and also to explore the odd ratios and the relationships strength between the categorical variables. Results: During the study period from march 2020 to September 2021 in Queen Alia hospital, Amman, Jordan, 718 adults inpatient confirmed with COVID-19 and included in this study according to the category, which 247 patients (31.6%) had suspected COVID-19 infection and 534 patients confirmed with infection (68.4%). the mean age of the patients in the whole study (59.40±10.60 years) and the non survivors have a mean age higher than survivors (the survivors younger than non survivors 58.35±10.20 years for survivors versus 59.66±10.69 years for non survivors) and the p value = 0.17. according to the gender the male distributed approximately (2.31: 1) compared to females (545 (69.8%) versus 236 (30.2%), respectively) and the p value = 0.829 67.7% of the men were affected (105 patients) while 32.3% of the women that affected (50 patients) were belong to non survivors cohort , compared to 70.3% (440 affected COVID-19 men) and 29.7% (186 affected COVID-19 women) were belonged to the Survivors Cohort. Conclusion: It is evident that there is a relationship between liver involvement in COVID-19 and mortality. Therefore, it is of the essence to adopt hepatic enzymes as a parameter in the assessment of patients with COVID-19 because of the effect of liver enzymes elevation on immune cells and subsequently the overall clinical impacts so it must to monitor the liver enzymes on daily bases for COVID-19 patients.

Keywords--coronavirus, COVID-19, gastrointestinal tract manifestations, SARS-CoV-2.

Introduction

The coronavirus 2019 (COVID-19) is global pandemic diseases that emerged in late 2019 and spread rapidly resulting in millions of deaths. The first series of cases were identified in Wuhan, Hubei Province, China. ¹⁻³ Since then, COVID- 19 has affected over 200 countries and infected over 527,631,000 people, with 6,282,602 deaths as of 25 May 2022. Virologically, coronaviruses, consisting of four genera (*Alpha-coronavirus*, *Beta-coronavirus*, *Gamma-coronavirus* and *Delta-coronavirus*). COVID-19 diseases are caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), a novel RNA virus, which belongs to the *Beta-coronavirus* genus. ⁴⁻⁶

Historically, over than 8400 people in at least 30 countries were infected by SARS-CoV-1 between 2002 and 2003. This coronavirus related infection was resulted in approximately 10% overall mortality rate.⁷⁻⁸ Ten years later, middle-east respiratory syndrome coronavirus (MERS-CoV) affected approximately 2182 cases over 27 countries with an overall 779 reported deaths count.⁹⁻¹⁰ In contrast to the SARS-CoV-1 and MERS-CoV related diseases, SARS-CoV-2 associated COVID-19 diseases have higher pathogenicity, transmissibility, severity, public

health threatening, and mortality.¹¹⁻¹³ Genetically, SARS-CoV-2 genome sequence shares approximately 50% and 75% identities with MERS-CoV and SARS-CoV-1, respectively. Notably, both genera of SARS employ host-cell angiotensin-converting enzyme 2 (ACE2) as a entry receptor, which is similarly used by SARS-CoV-1

While the respiratory symptoms are predominated in SARS-CoV-2 infected patients, other explored symptoms related organs, of particular the gastrointestinal, liver, endocrine, hematological, renal, immunological, dermatological, and cardiovascular systems, are also commonly encountered.¹⁴ In contrast to SARS-CoV-1 and MERS-CoV infection, gastrointestinal related SARS-CoV-2 infection are often appeared on early and may worsen during the infection pattern. Nausea, vomiting, diarrhea, and abdominal cramping are the most commonly reported gastrointestinal related symptoms in affected COVID-19 patients.¹⁵ Regarding coronaviruses infections related liver injuries, all aforementioned coronaviruses are commonly associated with liver diseases with an incidence rate of 15% to 75%.^{4,5} Sometimes, the COVID-19 infection related gastrointestinal symptoms could be the solely manifestation which delay diagnosis to first respiratory symptoms. While the actual mechanisms of gut and liver involvements in COVID-19 diseases still remain unclear, the widespread expression of ACE2 receptors in gastrointestinal tract facilitates viral entry to the cells.¹⁶⁻¹⁷

Biochemically, most patients show mild to moderate elevation of transaminases with slightly elevated bilirubin levels which are positively correlated with the severity of the disease. The three most routinely measured indexes for assessing COVID-19 related biochemical and clinical impacts on hepatocytes are lactate dehydrogenase (LDH), alanine transaminases (ALT), and aspartate transaminases (AST). Although higher AST and LDH levels are likely to associate with SARS-CoV-2 infected patients' mortality, there is still a lack of an adequate clinical studies on LDH/AST ratio on admission to predict disease course in COVID-19 patients. In this study, we described the clinical comparative outcomes, biochemical results, sensitivity analysis, and prognostic logistic regression modeling for admitted affected COVID-19 patients on isolation departments at Queen Alia Military Hospital, Royal Medical Services, Amman.

Method

This study was retrospectively conducted on. The study was reviewed and approved by the standing committee for coordination of health and medical research at the Royal Medical Services (Ref# 18_4/2022). Patient's data, including demographical, anthropometrical, biochemical, and nutritional data, were retrospectively retrieved from our electronic medical record system (Hakeem) over 19 months between Mar 2020 and Sep 2021. Studied patients who were below 18 years, whose hospital length of stay (LOS) didn't exceed 7 days, and whose studied variables were totally or partially missed were excluded from our study.

Owing to our study's retrospective design, a signed consent form was waived. All eligible studied patients had variable diseases severities, ranges from moderate to severe, including severe ARDS affected mechanically ventilated critically ill

patients. Based on PCR positivity, patients who had a negative PCR test but clinically, biochemically, and radiologically go with COVID-19 disease were considered as suspected SARS-CoV-2 infected patients while patients who had a positive PCR test were considered as confirmed SARS-CoV-2 infected patients. Both suspected and confirmed SARS-CoV-2 infected patients were included in our study. Hemodynamics variables of Shock Index (SI) and modified Shock Index (mSI) were mathematically retrieved after dividing heart rate to systolic blood pressure (SBP) and mean arterial pressure, retrospectively. Prognosticators' ratios, including c-reactive protein (CRP) to albumin ratio (CRP: ALB), ferritin to albumin ratio (FER: ALB), neutrophils to lymphocytes ratio (NLR), and monocytes to lymphocytes ratio (MLR) were also calculated from the primary retrievable data.

All retrievable and calculated variables were thereafter divided into parametric data and non-parametric for which the comparative parametric data were analyzed across the two studied groups, SARS-CoV-2 infected patients whose LDH: AST 1 was $<6.5: 1$ Cohort (Cohort I) and SARS-CoV-2 infected patients whose LDH: AST 1 was $\geq 6.5: 1$ Cohort (Cohort II) by Independent and One Sample T Tests to express the analysis results as either mean \pm SD or Mean difference \pm SEM. In other side of data, the non-parametric variables were analyzed using the Chi Square Test and the outcomes results were expressed as Number (Percentage) and the relative risk estimates were expressed as odd ratio (OD). All comparatively studied variables between SARS-CoV-2 infected patients whose LDH: AST 1 was $<6.5: 1$ Cohort (Cohort I) and SARS-CoV-2 infected patients whose LDH: AST 1 was $\geq 6.5: 1$ Cohort (Cohort II) among admitted affected COVID-19 patients at Queen Alia Military Hospital, Jordan between Mar 2020 and Sep 2021 were summarized in Table 1-3.

The Multivariate Logistic Regression Test was conducted to explore the degree of correlations, how much of the total variations in the dependent variable can be explained by the independent variables, and the quality of the prediction of the dependent variable. The Multivariate Logistic Regression Test was performed to ascertain the effects of gender, severity group at admission, and the primary our tested composite predictor, $\% \Delta$ FER: ALB to LMR₁₂, on the likelihood that admitted SARS-CoV-2 infected patients have liver diseases as signified by LDH: AST 1 ≥ 6.5 . Also, this test was conducted to abstract the necessary coefficients to collectively predict SARS-CoV-2 infected patients liver diseases status and to present the final form of our proposed multivariate logistic regression model for the affected COVID-19 patients.

The area under the receiver operating characteristic (ROC) analysis was constructed against the overall admitted SARS-CoV-2 infected patients who have liver diseases as signified by LDH: AST₁ ≥ 6.5 (1) vs LDH: AST₁ < 6.5 (0). Sensitivity analysis was processed on a total of 781 processed cases, 155-case were processed as positive actual state, and 626-case were processed as a negative actual state. 0 processed cases were dealt with as missing data. higher values of the test result variable(s) indicate stronger evidence for a positive actual state. The positive actual state is the admitted SARS-CoV-2 infected patients who have liver diseases as signified by LDH: AST₁ ≥ 6.5 . The optimal cut-off points, sensitivities, specificities, positive and negative predictive values, Youden and accuracy indices, and the negative likelihood ratios for LDH: AST₁ and LDH: AST

2 in prognosticating the likelihood that admitted SARS-CoV-2 infected patients have liver diseases as signified by LDH: AST 1 \geq 6.5.

Results

During the study period from March 2020 to September 2021 in Queen Alia hospital, Amman, Jordan, 718 adults inpatient confirmed with COVID-19 and included in this study according to the category, which 247 patients (31.6%) had suspected COVID-19 infection and 534 patients confirmed with infection (68.4%). the mean age of the patients in the whole study (59.40 \pm 10.60 years) and the non survivors have a mean age higher than survivors (the survivors younger than non survivors 58.35 \pm 10.20 years for survivors versus 59.66 \pm 10.69 years for non survivors) and the p value = 0.17. according to the gender the male distributed approximately (2.31: 1) compared to females (545 (69.8%) versus 236 (30.2%), respectively) and the p value = 0.829 67.7% of the men were affected (105 patients) while 32.3% of the women that affected (50 patients) were belong to non survivors cohort , compared to 70.3% (440 affected COVID-19 men) and 29.7% (186 affected COVID-19 women) were belonged to the Survivors Cohort all the data organized in table 1.

Oxygen supply strategies for the whole studied cohort were significantly distributed between Survivors Cohort (Cohort I) and Non-Survivors Cohort (Cohort II), in which 76 (9.7%), 332 (42.5%), 357 (45.7%), and 16 (2.0%) versus 76 (20.2%), 205 (54.5%), 95 (25.3%), and 0 (0.0%) were on non-O₂ supply, nasal canula at flow rate of 3-6 L/min, non-invasive mechanical ventilation, and invasive mechanical ventilation, retrospectively. Although the Survivors Cohort had significantly lower averaged human albumin intake than Non-Survivors Cohort [12 \pm 4 g/day vs 18 \pm 4 g/day, -7 \pm 0 g/day, p-value=0.00], the changes in serum albumin levels (% Δ ALB 12) were insignificant [44.8% \pm 12.9% vs 44.5% \pm 34.8%, 0.3% \pm 1.7%, p-value=0.843]. Average Paracetamol dose was significantly higher in Non-Survivors Cohort compared to Survivors Cohort [3.32 \pm 0.46 g/day vs 1.55 \pm 0.65 g/day, +1.77 \pm 0.06, p-value=0.00] in which the percentages distribution of Paracetamol IV compared to Paracetamol P.O in Non-Survivors Cohort [151 (97.4%) vs 132 (21.1%)] was significantly higher than in Survivors Cohort [4 (2.6%) vs 494 (78.9%)]. Prescribing antibiotics were allocated insignificantly between the two tested cohorts in which Survivors Cohort had non-Tazocin® and Tazocin® antibiotics of 323 (51.6%) and 303 (48.4%) compared 80 (51.6%) and 75 (48.4%) in Non-Survivors Cohort. According to estimated CrCl based on Jelliffe equation, Survivors Cohort had significantly lower %Deficit dosing in prescribing PIP/TAZ (Tazocin®) and IMI/CIL (Imipenem®) compared to Non-Survivors Cohort [-27.73% \pm 3.92% and -28.73% \pm 5.85% vs -30.21% \pm 4.06% and -38.67% \pm 8.13%, respectively, p-Value=0.00].

Average corrected sodium level (cNa₂) was significantly higher in Survivors Cohort compared to Non-Survivors Cohort [137.86 \pm 3.16 mEq/l vs 128.77 \pm 3.84 mEq/l, +9.09 \pm 0.30mEq/l, p-value=0.00] and the incidence of hyponatremia was significantly higher in Non-Survivors Cohort compared to Survivors Cohort [155 (100.0%) vs 471 (75.2%), retrospectively, p-value=0.00]. Survivors Cohort had insignificantly higher average blood glucose level (BG₂) than Non-Survivors Cohort [153.04 \pm 39.18 mg/dl vs 147.74 \pm 20.81 mg/dl; +5.30 \pm 3.26 mg/dl, p-

Value=0.10]. Oppositely, Survivors Cohort had significantly lower average total daily insulin dosing compared to Non-Survivors Cohort [31.74±1.80 IU/day vs 33.55±1.90 IU/day; -1.82±0.16 IU/day, p-Value=0.00] all organized in table 2 :

Hemodynamically, Survivors Cohort had significantly higher reduction rate in SI and mSI (% Δ SI and % Δ mSI, respectively) than Non-Survivors Cohort [-25.3%±11.8% and -31.2%±11.3% vs -0.9%±6.0% and -7.5%±6.0%, respectively, p-value=0.00]. SARS-CoV-2 infected patients in Non-Survivors Cohort had significantly higher bilirubin levels and INR than in Survivors Cohort [2.71±0.16 mg/dl and 2.68±0.11 vs 2.53±0.18 mg/dl and 2.57±0.11, respectively, p-value=0.00]. Unexpectedly, the nutritional indices inputs of total calories (TCI) and protein densities (PD) were significantly lower in Survivors Cohort compared to Non-Survivors Cohort [523.2±192.7 Cal/day and 1.92±1.03 g/100 Cal vs 766.9±208.0 Cal/day and 2.56±0.73 Cal, respectively, p-value=0.00] and carbohydrate densities were significantly higher in Survivors Cohort compared to Non-Survivors Cohort [20.62±4.70 g/100 Cal vs 17.71±3.39 g/100 Cal; 2.91±0.40 g/100 Cal, p-Value=0.00]. Haematologically, the reduction percentages in white blood cells counts, absolute neutrophils counts, monocytes counts, neutrophils to lymphocytes ratios, and monocytes to lymphocytes ratios (% Δ WBCs12 , % Δ ANC12, % Δ MC12, % Δ NLR12 and % Δ MLR12) were significantly higher in Survivors Cohort compared to Non-Survivors Cohort [-26.9%±28.7%, -41.4%±30.6%, 51.7%±37.3%, -48.0%±15.2%, and -58.3%±12.8% vs +36.0%±15.8%, +22.9%±14.7%, +27.1%±18.0%, +23.7%±146.0%, and -6.9%±103.3%, respectively, p-Value=0.000]. Regarding prognosticator biomarkers and their ratios, the reduction percentages in FER: ALB and CRP: ALB (% Δ FER: ALB 12 and % Δ CRP: ALB 12 , respectively) were also significantly higher in Survivors Cohort compared to Non-Survivors Cohort [-62.9%±13.0% and -63.7%±12.7% vs -39.1%±8.1% and -41.8%±8.3%, respectively, p-value=0.00]. In addition to the investigated overall mortality and overall survival rates in our study [(N=155, 19.85%) and (N=626, 80.15%)], we also investigated the overall hospital length of stay (LOS) which it was significantly lower in Non-Survivors Cohort compared to Survivor Cohort [10.45±2.08 days vs 11.42±2.98 days, respectively, p-Value=0.00]. There were insignificant differences between the two studied cohorts regarding their baseline anthropometrics (all organized in table 3)

Discussion

In the present study which analyzed data obtained from the data base of the Queen Alia hospital the patients in the isolation center divided into 2 cohorts , cohort 2 (non survivors) and chort 1(survivors) , and the study ranged from march 2020 to september 2021 . To the best of our knowledge, the uniqueness of our study is primarily involved in its multi-faceted comparative variables, including but not excluded to, anthropometrical, biochemical hemodynamical, hematological, and prognostical tested variables in addition to our tested prognosticator of hyperglycemia among the Survivors and Non-Survivors Cohorts. Several systematic reviews and meta-analysis studies examine risk factors associated with overall negative clinical impacts in affected COVID-19 patients. However, most of these studied patients in these studies had not progressed to the study endpoints by the time the study was conducted, in

addition to the their relatively small sample sizes which leading to bias and unreliabl prediction for COVID-19 disease progression and overall SARS-CoV-2 infected patients' mortalities. (16-19)

As well known, T cells were found to be mandatory for virological clearance of SARS-CoV in already infected cells, including MERS-CoV, SARS-CoV 1, SARS-CoV 2. And observational studies have also shown a strong negative correlation between total lymphocytes counts (TLC) and overall clinical outcomes. 20-21 A study of 138 hospitalized SARS-CoV-2 infected patients in Wuhan, China, found that prolonged and severe lymphopenia accompanied with leukocytosis was associated with higher mortality. 22 As previously mentioned in this study, affected COVID-19 patients are likely to have a dysfunctional immunity on white blood cells, particularly lymphocytes and macrophages, that may be linked to significantly higher incidences of in-hospital complications and multiple organ failures in moderate-severe admitted SARS-CoV-2 infected patients with uncontrolled hyperglycemia. This is consistent with previous reports that a high glucose level have been linked to significantly higher COVID-19 associated ARDS complications in severe SARS-CoV-2 infected patients. Also, relatively prolonged uncontrolled in blood glucose levels are substantially contributes to other comorbidities, including but not excluded to, peripheral arteriosclerosis, ketoacidosis, and progression of diabetic nephropathy, which all are also related to overall affected COVID-19 patients' mortalities. 23-24 Although in our study, the average blood glucose levels were higher in Survivors Cohort compared to Non-Survivors Cohort by $+5.30\pm 3.26$ mg/dl, this mean difference \pm SEM was insignificant, and alternatively we investigated that the average total insulin dosing in Survivors Cohort was significantly lower than in Non-Survivors Cohort by -1.82 ± 0.16 IU/day. Though, the underlying mechanisms of hyperglycemia related COVID-19 disease morbidity and mortality are currently unclear, many emerging proposed evidences link between hyperglycemia and higher propensity for angiotensin-converting enzyme-2 (ACE-2) receptors expression in SARS-CoV-2 infected patients, making them vulnerable for the virus binding and entrance. Effective glycemic monitor and management may be beneficial to reduce the progression and fatality of COVID-19 patient. 25-27 In this study, we explored that the 3 tested BG related prognosticators for SARS-CoV-2 infected patients mortality, may be used for early prediction of COVID-19 disease progression with high sensitivity, specificity, and accuracy values, especially for changes in BG from baseline (% Δ BG12).

Due to the absence, so far, of a defined treatment for infection by the novel coronavirus, since it is still necessary to demonstrate the effectiveness of what has already been proposed, the therapeutic approach to this disease involves the administration of drugs that favor the hepatotoxic potential, such as oseltamivir, hydroxychloroquine, paracetamol and acetaminophen ^(44,55). Therefore, the importance of studies on the relationship between the liver and COVID-19 is evident, so that health professionals, having this knowledge, can reduce the risk in their patients and thus avoid death due to liver damage from COVID-19. ⁵⁶

Conclusion

It is evident that there is a relationship between liver involvement in COVID-19 and mortality. Therefore, it is of the essence to adopt hepatic enzymes as a parameter in the assessment of patients with COVID-19 because of the effect of liver enzymes elevation on immune cells and subsequently the overall clinical impacts so it must to monitor the liver enzymes on daily bases for COVID-19 patients. This study is limited by its retrospective design. A larger, multisite, and prospective study is needed to control for multiple confounders. Despite these limitations, our conclusions may have an added value to the current excessively evolving controversial pieces of evidence. A larger, multisite, and prospective study is needed to control for multiple confounders. Despite these limitations, our conclusions may have an added value to the current excessively evolving controversial pieces of evidence.

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Table 1

Comparatively studied variables between SARS-CoV-2 infected patients whose LDH: AST₁ was <6.5: 1 Cohort (Cohort I) and SARS-CoV-2 infected patients whose LDH: AST₁ was ≥6.5: 1 Cohort (Cohort II) among admitted affected COVID-19 patients at Queen Alia Military Hospital, Jordan between Mar 2020 and Sep 2021

Studied Comparative Variables		Overall Cohorts (N=781) Mean±SD	Cohort I (N= 392, 50.19%) Mean±SD	Cohort II (N=389, 49.81%) Mean±SD	Mean Diff±SEM or OD	P-Value
Gender	F	236 (30.2%)	151 (38.5%)	85 (21.9%)	2.24 (95% CI; 1.64-3.07)	0.000
	M	545 (69.8%)	241 (61.5%)	304 (78.1%)		
	M: F ratio	2.31: 1	1.6: 1	3.58: 1		
COVID-19 case	Suspected	247 (31.6%)	119 (30.4%)	128 (32.9%)	0.89 (95% CI; 0.66-1.20)	0.444
	Confirmed	534 (68.4%)	273 (69.6%)	261 (67.1%)		
FCR ₁		12.48±1.12	12.52±0.50	12.43±1.50	0.08±0.08	0.312

FCR ₂	14.41±3.46	13.44±0.93	15.38±4.62	-1.94±0.24	0.000
FER ₁	746.5±310.7	714.0±194.5	779.3±392.1	-65.3±22.1	0.003
ALB ₁ (g/dl)	2.21±0.38	2.23±0.35	2.18±0.40	0.06±0.03	0.033
FER: ALB ₁	362.1±206.2	337.27±123.72	387.14±262.26	-49.87±14.66	0.001
CRP ₁ (mg/dl)	59.65±22.74	56.91±15.06	62.41±28.21	-5.49±1.62	0.001
CRP: ALB ₁	28.83±15.11	26.83±9.58	30.85±18.92	-4.02±1.07	0.000
FER ₂ (ng/ml)	855.1±503.0	769.4±333.7	941.5±617.8	-172.0±35.5	0.000
ALB ₂ (g/dl)	3.19±0.64	3.19±0.57	3.18±0.71	0.02±0.05	0.729
FER: ALB ₂	298.9±233.0	261.23±139.83	336.81±294.13	-75.58±16.46	0.000
CRP ₂ (mg/dl)	56.88±24.55	56.54±23.49	57.21±25.60	-0.67±1.76	0.704
CRP: ALB ₂	19.62±11.46	19.15±9.93	20.09±12.82	-0.94±0.82	0.250
%ΔFER: ALB ₁₂	-23.9%±28.1%	-27.5%±20.0%	-20.2%±33.9%	-7.2%±2.0%	0.000
%ΔCRP: ALB ₁₂	-34.7%±18.0%	-32.6%±18.0%	-36.8%±17.8%	4.1%±1.3%	0.001
%ΔFCR ₁₂	14.2%±17.8%	7.3%±4.5%	21.2%±22.8%	-13.9%±1.2%	0.000

The Non-categorical data results of the comparative variables between the Cohort I and Cohort II were statistically analyzed by independent T and One-Sample T-Test (at p-value< 0.05) and expressed as Mean±SD and Mean difference±SEM. While the categorical data results of the comparative variables between the 2 tested cohorts were statistically analyzed by Chi Square Test (at p-value< 0.05) and expressed as Number (Percentage). Also, the Chi Square Test was used to explore the association strength between the dichotomous comparative tested variables.

➤ Cohort I: Admitted SARS-CoV-2 infected patients whose LDH: AST₁ was <6.5: 1.

➤ Cohort II: Admitted SARS-CoV-2 infected patients whose LDH: AST₁ was ≥6.5: 1

FCR₁: Baseline ferritin to c-reactive protein ratio.

FCR₂: Ferritin to c-reactive protein ratios average during admission.

FER: ALB₁: Baseline ferritin to albumin ratio.

FER: ALB₂: Ferritin to albumin ratios average during admission.

CRP: ALB₁: Baseline c-reactive protein to albumin ratio.

CRP: ALB₂: C-reactive protein to albumin ratios average during admission.

%ΔFER: ALB₁₂: Percentage changes of ferritin to albumin ratios.

%ΔCRP: ALB₁₂: Percentage changes of c-reactive protein to albumin ratios.

%ΔFCR₁₂: Percentage changes of ferritin to c-reactive protein ratios.

%TLC₁₂: Percentage changes of total lymphocyte counts.

FER₁: Baseline ferritin level.

ALB₁: Baseline albumin level.

CRP₁: Baseline c-reactive protein level.

FER₂: Ferritin levels average during admission.

ALB₂: Albumin levels average during admission.

CRP₂: C-reactive protein levels average during admission.

F: Female.

M: Male.

M: F: Male to Female ratio.

Significant: (P-Value <0.05).

Table 2

Comparatively studied variables between SARS-CoV-2 infected patients whose LDH: AST₁ was <6.5: 1 Cohort (Cohort I) and SARS-CoV-2 infected patients whose LDH: AST₁ was ≥6.5: 1 Cohort (Cohort II) among admitted affected COVID-19 patients at Queen Alia Military Hospital, Jordan between Mar 2020 and Sep 2021

Studied Comparative Variables		Overall Cohorts (N=781) Mean±SD	Cohort I (N=392, 50.19%) Mean±SD	Cohort II (N=389, 49.81%) Mean±SD	Mean Diff±SEM or OD	P-Value
COVID-19 severity	Mild-Moderate	393 (50.3%)	190 (48.5%)	203 (52.2%)	0.86 (95% CI; 0.65-1.14)	0.299
	Severe-Critical	388 (49.7%)	202 (51.5%)	186 (47.8%)		
Dex	None	376 (48.1%)	179 (45.7%)	197 (50.6%)	0.82 (95% CI; 0.62-1.09)	0.164
	Yes	405 (51.9%)	213 (54.3%)	192 (49.4%)		
O ₂ supply	None	177 (22.7%)	109 (27.8%)	68 (17.5%)	NA	0.000
	NC (3-6 L/min)	223 (28.6%)	96 (24.5%)	127 (32.6%)		
	NIMV	203 (26.0%)	116 (29.6%)	87 (22.4%)		
	IMV	178 (22.8%)	71 (18.1%)	107 (27.5%)		
HALB (g/day)		81.8±38.1	74.84±25.24	88.73±46.66	-13.89±2.68	0.000

HLOS (days)	11.6±1.6	11.33±1.13	11.88±1.91	-0.55±0.11	0.000
Age (age)	59.4±10.6	59.68±10.62	59.12±10.60	0.57±0.76	0.457
BW (Kg)	73.7±10.0	73.28±9.73	74.18±10.30	-0.90±0.72	0.209
BMI (Kg/m ²)	25.95±3.89	26.08±3.95	25.81±3.83	0.27±0.28	0.325
Tavg ₁ (° C)	37.64±0.95	37.43±0.81	37.86±1.03	-0.43±0.07	0.000
Tavg ₂ (° C)	36.86±1.26	36.67±0.50	37.04±1.70	-0.37±0.09	0.000
Insulin IU/hr	1.34±0.09	1.34±0.09	1.33±0.08	0.01±0.01	0.385
%WBC ₁₂	14.7%±24.6%	18.5%±25.4%	10.9%±23.0%	7.6%±1.7%	0.000
%MLR ₁₂	-69.6%±27.4%	-76.1%±12.1%	-63.0%±35.7%	-13.1%±1.9%	0.000
%ΔFER: ALB to LMR ₁₂	-72.2%±33.8%	-82.7%±9.5%	-61.6%±44.5%	-21.0%±2.3%	0.000
%ΔCRP: ALB to LMR ₁₂	-76.0%±32.0%	-71.0%±42.4%	-81.0%±14.0%	10.0%±2.3%	0.000
%ΔBUNSCr ₁₂	-32.8%±15.8%	-36.3%±17.3%	-29.2%±13.1%	-7.2%±1.1%	0.000
CrCl _{Jelliffe eq}	48.56±5.45	49.73±1.65	47.37±7.36	2.36±0.38	0.000

The Non-categorical data results of the comparative variables between the Cohort I and Cohort II were statistically analyzed by independent T and One-Sample T-Test (at p-value < 0.05) and expressed as Mean±SD and Mean difference±SEM. While the categorical data results of the comparative variables between the 2 tested cohorts were statistically analyzed by Chi Square Test (at p-value < 0.05) and expressed as Number (Percentage). Also, the Chi Square Test was used to explore the association strength between the dichotomous comparative tested variables.

- Cohort I: Admitted SARS-CoV-2 infected patients whose LDH: AST 1 was <6.5: 1.
- Cohort II: Admitted SARS-CoV-2 infected patients whose LDH: AST 1 was ≥6.5: 1

%WBC ₁₂ : Percentage changes of white blood cells.	BMI: Body mass index in Kg per m ² .
%TLC ₁₂ : Percentage changes of total lymphocyte counts.	T _{avg1} : Baseline average core body temperatures in ° C.
%MC ₁₂ : Percentage changes of monocyte counts.	T _{avg2} : Average Core body temperatures in ° C.
%MLR ₁₂ : Percentage changes of monocyte to lymphocyte ratios.	Insulin _{rate} : Insulin infusion rate in IU/hr.
%ΔFER: ALB to LMR ₁₂ : Percentage changes of FER: ALB to reverse MLR.	HALB: Human albumin 20% inputs average in g/day.
%ΔCRP: ALB to LMR ₁₂ : Percentage changes of CRP: ALB to reverse MLR.	HLOS: Hospital length of stay days.
%ΔBUNSCr ₁₂ : Percentage changes of BUN to SCr.	CrCl _{Jelliffe eq} : Creatinine clearance based on Jelliffe eq.
NC: Nasal canula on oxygen flow rate of 3-6 L/min.	Dex: Dexamethasone.
NIMV: Non-invasive mechanical ventilation.	NA: Not statistically applicable and can't be computed.
IMV: Invasive mechanical ventilation.	N: Number of tested COVID-19 patients.

Table 3

Comparatively studied variables between SARS-CoV-2 infected patients whose LDH: AST₁ was <6.5: 1 Cohort (Cohort I) and SARS-CoV-2 infected patients whose LDH: AST₁ was ≥6.5: 1 Cohort (Cohort II) among admitted affected COVID-19 patients at Queen Alia Military Hospital, Jordan between Mar 2020 and Sep 2021

Studied Comparative Variables	Overall Cohorts (N=781) Mean±SD	Cohort I (N=392, 50.19%) Mean±SD	Cohort I (N=389, 49.81%) Mean±SD	Mean Diff±SEM or OD	P-Value
Bil ₁ (mg/dl)	1.30±0.89	1.22±0.36	1.38±1.20	-0.15±0.06	0.016
Bil ₂ (mg/dl)	1.74±1.07	1.62±0.41	1.87±1.44	-0.25±0.08	0.001
ALT ₁ (IU/L)	32.63±16.85	30.04±5.95	35.25±22.83	-5.20±1.19	0.000
ALT ₂ (IU/L)	35.40±21.46	31.70±7.18	39.13±29.09	-7.42±1.51	0.000
AST ₁ (IU/L)	38.27±13.24	37.31±4.91	39.23±18.07	-1.91±0.95	0.043
AST: ALT ₁	1.29±0.24	1.26±0.09	1.32±0.33	-0.07±0.02	0.000
AST ₂ (IU/L)	43.94±17.52	41.92±6.04	45.98±23.92	-4.07±1.25	0.001
AST: ALT ₂	1.45±0.40	1.35±0.12	1.56±0.54	-0.21±0.03	0.000
LDH ₁ (IU/L)	253.91±97.42	232.19±40.43	275.80±128.35	-43.61±6.80	0.000
LDH: AST ₁	6.60±0.46	6.19±0.27	7.01±0.05	-0.82±0.01	0.000
LDH ₂ (IU/L)	265.26±105.99	241.40±42.65	289.31±139.98	-47.91±7.39	0.000

LDH: AST ₂	6.09±0.45	5.73±0.21	6.44±0.32	-0.71±0.02	0.000
PT ₁ (seconds)	11.51±1.27	11.40±0.84	11.62±1.58	-0.22±0.09	0.015
PT ₂ (seconds)	12.82±1.81	12.56±0.98	13.07±2.34	-0.51±0.13	0.000
aPTT ₁ (seconds)	32.20±5.30	32.06±2.91	32.33±6.92	-0.27±0.38	0.476
aPTT ₂ (seconds)	35.64±6.35	35.21±3.17	36.08±8.40	-0.87±0.45	0.054

The Non-categorical data results of the comparative variables between the Cohort I and Cohort II were statistically analyzed by independent T and One-Sample T-Test (at p-value < 0.05) and expressed as Mean±SD and Mean difference±SEM. While the categorical data results of the comparative variables between the 2 tested cohorts were statistically analyzed by Chi Square Test (at p-value < 0.05) and expressed as Number (Percentage). Also, the Chi Square Test was used to explore the association strength between the dichotomous comparative tested variables.

- Cohort I: Admitted SARS-CoV-2 infected patients whose LDH: AST₁ was <6.5: 1.
- Cohort II: Admitted SARS-CoV-2 infected patients whose LDH: AST₁ was ≥6.5: 1

Bil ₁ : Baseline bilirubin level levels in mg per dl. Bil ₂ : Bilirubin levels averages during admission in mg/dl. ALT ₁ : Baseline Alanine aminotransferase levels in IU per L. ALT ₂ : Alanine transferase levels average during admission in IU per L. AST ₁ : Baseline aspartate aminotransferase levels in IU per L. AST: ALT ₁ : Baseline AST to ALT ratio. AST ₂ : Aspartate aminotransferase levels average in IU per L. AST: ALT ₂ : AST to ALT ratios average during admission.	LDH ₁ : Baseline Lactate dehydrogenase level in IU/L. LDH: AST ₁ : Baseline LDH to AST ratio. LDH ₂ : Lactate dehydrogenase levels average in IU/L. LDH: AST ₂ : LDH to AST ratios average while admission. PT ₁ : Baseline prothrombin time in seconds. PT ₂ : Prothrombin times average while admission in seconds. aPTT ₁ : Baseline activated partial thromboplastin time. aPTT ₂ : Activated partial thromboplastin times average.
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Table 4

Multivariate Logistic Regression results for the 5 tested variables regarding SARS-CoV-2 infected patients' liver diseases risk as illustrated by elevation LDH: AST₁ above 6.5 on Queen Alia Military Hospital, Jordan between Mar 2020 and Sep 2021

Tested predictors	B±SEM	Wald	df	Sig.	Exp(B)	95% C.I. for EXP(B)	
						Lower	Upper
Gender	0.756±0.186	16.442	1	0.000	2.130	1.478	3.069
Age (Yrs)	-0.011±0.008	1.903	1	0.168	0.989	0.974	1.005
BMI (Kg/m ²)	-0.003±0.021	0.023	1	0.879	0.997	0.956	1.039
Severity Group	-1.8660.227	67.480	1	0.000	0.155	0.099	0.241
%Δ FER: ALB to LMR 12	0.057±0.006	92.582	1	0.000	1.059	1.047	1.071
Constant	5.425±0.953	32.421	1	0.000	226.990		

- ❖ The Multivariate Logistic Regression Test was conducted to explore the degree of correlations, how much of the total variations in the dependent variable can be explained by the independent variables, and the quality of the prediction of the dependent variable.
- ❖ The logistic regression model was statistically significant, $\chi^2(8) = 146.822, p < .0005$. The explained variation in the dependent variable based on our model ranges from 22.3% to 29.7%, depending on whether you reference the Cox & Snell R² or Nagelkerke R² methods, respectively, and correctly classified 67.1% of cases.
- ❖ The Multivariate Logistic Regression Test was performed to ascertain the effects of gender, severity group at admission, and the primary our tested composite predictor, %Δ FER: ALB to LMR₁₂, on the likelihood that admitted SARS-CoV-2 infected patients have liver diseases as signified by LDH: AST₁ ≥6.5. Also, this test was conducted to abstract the necessary coefficients to collectively predict SARS-CoV-2 infected patients liver diseases status and to present the final form of our proposed multivariate logistic regression model for the affected COVID-19 patients which can be formulated as follows.

likelihood that admitted SARS-CoV-2 infected patients have liver diseases as signified by LDH: AST₁ ≥6.5
 $= e^{(5.425+0.756 \times \text{Gender} + 0.057 \times \% \Delta \text{FERALB: LMR}_{12} - 1866.23 \times \text{Severity Group})} / (1 + e^{(5.425+0.756 \times \text{Gender} + 0.057 \times \% \Delta \text{FERALB: LMR}_{12} - 1866.23 \times \text{Severity Group})})$

- Cohort I: Admitted SARS-CoV-2 infected patients whose LDH: AST₁ was <6.5: 1.
- Cohort II: Admitted SARS-CoV-2 infected patients whose LDH: AST₁ was ≥6.5: 1
- %Δ FER: ALB to LMR₁₂: Percentage changes of Ferritin: Albumin to Lymphocytes: Monocyte's ratio from baseline admission level.
- Severity Group: SARS-CoV-2 infected patients' severities on admission which categorized into either Mild/Moderate or Severe/Critical.

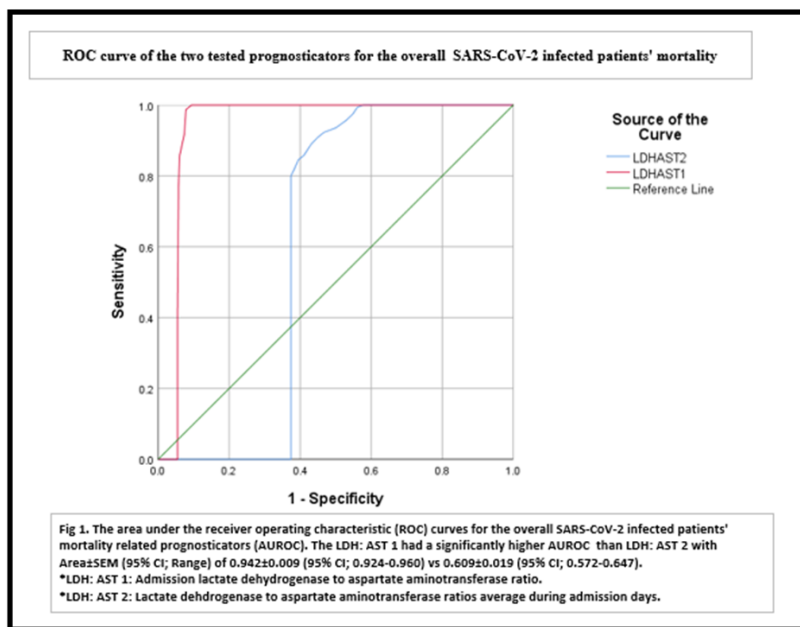


Table 5

The optimal cut-off points, sensitivities, specificities, positive and negative predictive values, Youden and accuracy indices, and the negative likelihood ratios for LDH: AST₁ and LDH: AST₂ in prognosticating the likelihood that admitted SARS-CoV-2 infected patients have liver diseases as signified by LDH: AST₁ ≥6.5

Prognostic Indicator	Cutoff	TPR	FPR	YI	TNR	PPV	NPV	NLR	AI
LDH: AST ₁	7.0050	98.7%	7.8%	90.88%	92.17%	75.74%	99.65%	1.40%	93.47%
LDH: AST ₂	5.9750	91.0%	45.0%	45.92%	54.95%	33.33%	96.09%	16.44%	62.10%

➤ The area under the receiver operating characteristic (ROC) analysis was constructed against the

overall admitted SARS-CoV-2 infected patients who have liver diseases as signified by LDH: AST₁ ≥6.5 (1) vs LDH: AST₁ <6.5 (0). Sensitivity analysis was processed on a total of 781 processed cases, 155-case were processed as positive actual state, and 626-case were processed as a negative actual state. 0 processed cases were dealt with as missing data. higher values of the test result variable(s) indicate stronger evidence for a positive actual state. The positive actual state is the admitted SARS-CoV-2 infected patients who have liver diseases as signified by LDH: AST₁ ≥6.5.

- LDH: AST₁: Admission lactate dehydrogenase to aspartate aminotransferase ratio.
- LDH: AST₂: Lactate dehydrogenase to aspartate aminotransferase ratios average during admission days.

TPR: True positive rate (sensitivity).

FPR: False positive rate.

YI: Youden index.

TNR: True negative ratio (specificity).

PPV: Positive predictive value.

NPV: Negative predictive value.

NLR: Negative likelihood ratio.

AI: Accuracy index.