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Kidney and Liver Predictors of Adults Hospitalized with COVID-19 Infection

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Abstract: SARS-CoV-2 damages not only the lungs, but also the liver and kidney. Most critically ill COVID-19 patients have liver and kidney dysfunctions. The early identification of patients with COVID-19 who will develop severe or critical disease symptoms is important for delivering proper and early treatment. This research studies the correlation of liver and kidney function indexes and COVID-19 outcomes. Electronic medical record data from 391 patients diagnosed with COVID-19 in the COVID-19 Department, Galilee Medical Center, Nahariya, Israel were collected. Epidemiological, clinical, laboratory, and imaging variables were analyzed. The liver and kidney enzyme indexes were measured upon admission and discharge. A correlation between laboratory levels and severity and mortality of COVID-19 patients was undertaken. This study included 391 COVID-19 patients, 258 mild patients and 133 severe patients. Multivariate stepwise regression analyses and discriminant analyses were used to identify and validate powerful predictors. The main outcome was death or invasive ventilation. Three factors, namely higher urea nitrogen (BUN) and IL-6, and lower albumin levels, were the most powerful predictors of mortality, and classified the results (survival vs. death) correctly in 85% of cases (diagnostic accuracy) with a sensitivity of 88% and a specificity 55%. Compared with mild patients, severe patients had lower albumin (ALB), higher alanine aminotransferase (ALT), aspartate aminotransferase (AST) and BUN (all $p < 0.001$). COVID-19 patients, especially severe patients, have damage to liver and kidney function. BUN, IL-6 and albumin are factors predicting mortality while fibrinogen and AST could be independent factors for predicting the severity of COVID-19.

Keywords: pneumonia; COVID-19; liver enzymes; liver function tests (LFT); kidney function tests; risk factors; outcome; severity and mortality; SAR-CoV-2

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1. Introduction

The coronavirus disease 2019 (COVID-19) caused by the Severe Acute Respiratory Syndrome Corona Virus 2 (SARS-CoV-2) is the most recent pandemic and has greatly impacted social and human health issues [1]. Previous studies revealed that SARS-CoV-2 uses the angiotensin-converting enzyme 2 (ACE2) receptor to enter the lungs [2,3] which can cause severe lung fibrosis and consolidation, resulting in high mortality rates in severe cases [4,5]. Further studies have demonstrated that this virus can also damage the liver [6–10] and kidneys [11–14], since ACE2 is also expressed in both organs [15]. Other possible associated mechanisms of liver and kidney damage include the inflammatory cytokine storm [1,5,16–18], drug-induced injury [14,19–23], chronic liver and kidney disease [24–27] and other factors such as hemodynamic changes [28,29].

A recent study conducted in our department reported an increase risk of morbidity and/or mortality of COVID-19 with the association of age, neutrophil to lymphocyte ratio, BUN and the use of high-flow oxygen therapy.

Studies show the liver injury incidence of COVID-19 patients range from 14.8% to 53%, mainly presented by abnormal laboratory indexes including alanine aminotransferase (ALT), aspartate aminotransferase (AST), albumin (ALB), lactatedehydrogenase (LDH) and gamma-glutamyltransferase (GGT) [9,22,30,31]. Moreover, the severe cases are more likely to have severe liver injury than mild cases [7,32]. In addition, kidney involvement is common in COVID-19 patients who usually present with proteinuria. Severe patients are prone to present with sepsis-related acute kidney injury (AKI) and hypo perfusion-related AKI [24]. COVID-19 combined with kidney damage is an independent risk factor for poor prognosis and is associated with high mortality rates in the ICU [24,33]. So far, there has been little discussion about early monitoring of liver and kidney function to predict the patient's condition changes, thereby reducing mortality.

We aimed to investigate whether liver and kidney indices can predict severity and mortality in COVID-19 patients.

2. Methods

This is an analytical study. The relevant data regarding the patients were received and recorded in the medical files prospectively, but their use and analysis was performed retrospectively.

2.1. Study Population

A total of 391 COVID-19 patients were analyzed using the Electronic Medical Records (EMRs) between November 2020 and June 2021, in the COVID-19 department in the Galilee Medical Center.

2.2. Inclusion Criteria

(1) Age > 18 years.
(2) COVID-19 positive in real-time PCR assay.
(3) Hospitalized in COVID-19 internal medicine department.

2.3. Exclusion Criteria

(1) Pregnant woman.

2.4. Data Collection

We performed a retrospective analysis using the EMR data. The analyzed parameters were demographic features, prior and present medical status, clinical features, laboratory tests and treatments upon hospitalization. The diagnosis of COVID-19 was confirmed by positive real-time PCR assays from nasal and nasopharyngeal swab specimens.

2.5. Laboratory Measurements

Liver enzyme levels (AST, ALT) were measured by the International Federation of Clinical Chemistry (IFCC) method, while synthetic function (Albumin) was measured by the colorimetric (with bromocresol green) method. Ferritin was quantitatively measured using the chemiluminescent microparticle immunoassay (CMIA). Fibrinogen was automatically calculated using the HemosIL reagents. IL-6 was quantitatively determined by the electrochemiluminescence immunoassay (ECLIA). BUN was calculated using urease with an enzymatic procedure.

2.6. Definitions

We used the definition of cytokine storm reported by Carucchio et al. [19]. We categorized the severity of the disease as follows; mild disease, with mild clinical symptoms and no pneumonia manifestations in imaging; moderate disease, a patient has symptoms such as fever and respiratory tract symptoms and pneumonia manifestations can be seen in imaging. Severe patients were those who met any of the following criteria: oxygen saturation $\leq$ 93% at a resting state, respiratory rate $\geq$ 30 breaths/min, arterial partial

pressure of oxygen (PaO_2)/oxygen concentration (FiO_2) $\leq$ 300 mm Hg, patients requiring mechanical ventilation, shock presence, other organ failure requiring monitoring and treatment in the intensive care unit [34]. Liver injury patients were defined as follows: liver function examination with one or more of the following abnormalities during treatment: ALT > 40 u/l, AST > 40 u/l, ALB < 2.6 g/dL and INR > 1.8. The kidney injury patients were defined as follows; BUN > 7.1 mmol/L or creatinine (Cr) > 106 mol/L.

2.7. Ethics

Our medical center's local ethics committee approved this study (N 231-20). Retrospective analysis of data from our EMR database was performed under the oversight of the ICH guidelines for good clinical practice.

2.8. Outcomes

We defined severity using the 4-C score [35,36]. Critical COVID-19 was defined if one of the following criteria were met: admissions to ICU, the need of mechanical ventilation, ARDS or death.

2.9. Statistical Analysis

WinSTAT statistical analysis was performed. It is the statistical add-on program for Microsoft Excel. Univariate direct regression analysis and multivariate stepwise regression analysis were performed for individual variables, including clinical and biochemical variables as independent variables, and severity or death as dependent variables. For categorical variables, the frequency and corresponding diagnosis percentage are provided. Diagnostic analysis used to check the percentage of correct classification of the powerful predictors. Results are presented as mean + SD for continuous variables. Tests of significance were two-tailed, with a significance level set at $p < 0.05$.

3. Results

3.1. Patients' Characteristics

EMR data of 391 patients were collected (summarized in Table 1). The average age was 61, 149 (47%) male patients were in the survivor group and 60% were non-survivors. Ethnically Arab patients were twice as likely to be in the survivor group than patients of Jewish ethnicity. The opposite ratio was true in the non-survivors group. Comorbidities were much higher in the non-survivor group, with the most frequent ones being diabetes (57%), hypertension (84%), and hemodialysis (15%). Fever and dyspnea had the same percentages in both groups (57% and 59%, respectively). Diarrhea was threefold higher in the survivor group than in the non-survivors (6%, 2%, respectively). In lab results, statistical significance was seen in lymphocyte counts with lower values in the non-survivor group, 1.4 $\pm$ 4 versus 2.06 $\pm$ 11 in the survivor group. BUN values (40 $\pm$ 27) in the non-survivors were double than in in survivor group (19 $\pm$ 14). In addition, there were increased CRP values in the non-survivors (109) compared to the survivors (68). D-DIMER levels were also higher in the non-survivors (2539) in comparison with the survivors (1664). IL-6 was more in the non-survivors than in the survivors (264 $\pm$111, 34 $\pm$ 52, respectively). Higher ALT values were seen in non-survivors in comparison to survivors (37 $\pm$ 51, 23 $\pm$21) and albumin levels were lower in the non-survivors with an average of 3.4 (Table 1).

Table 1. Clinical characteristics of the surviving and non-surviving patients with COVID-19 infection.

Variable	**Survivors**	**Non-Survivors**	***p*-Value**
Total	N = 318	N = 74	
Age	58 ± 18	78 ± 12	0.001
Male (%)	0.47	0.6	600
Ethnicity % (Arab/Jewish)	(65/35)	(40/60)	0.004
BMI	29 ± 6	32 ± 11	0.008
Comorbidities %			
Diabetes (%)	30	57	0.001
Hypertension (%)	48	84	0.001
Lung disease (%)	9	18	0.03
Hemodialysis (%)	5	15	0.003
Aspirin use (%)	30	61	0.001
Symptom's duration before admission to hospitals	6 ± 5	9 ± 12	0.19
Fever %	57	56	0.77
Diarrhea %	6	2	0.26
Dyspnea %	59	59	0.74
Clinical severity on admission %	30	54	0.001
Lab Findings upon admission			
Hemoglobin (mg/dl)	13 ± 3	12 ± 1.2	0.06
Absolute neutrophil count ($\times 10^3/\mu L$)	13 ± 9	13 ± 6	0.9
Absolute lymphocyte count ($\times 10^3/\mu L$)	2.06 ± 11	1.4 ± 4	0.001
Neutrophil to lymphocyte ratio (NLR)	7.01 ± 3	9.1 ± 0.8	0.001
Platelet ($\times 10^3/\mu L$)	220± 86	220 ± 90	0.79
BUN (mg/dl)	19 ± 14	40 ± 27	0.001
Creatinine (mg/dl)	2 ± 8	2.2 ± 2	0.7
Triglycerides (mg/dl)	145 ± 148	157 ± 48	0.08
HDL (mg/dl)	33 ± 12	30 ± 13	0.09
Insulin Resistance (TG/HDL)	5.4 ± 5.8	6.1 ± 5.0	0.02
C-reactive protein (CRP) (mg/dl)	68 ± 78	109 ± 97	0.001
Ferritin	632 ± 987	1041 ± 3594	0.57
D-dimer	1664 ± 3513	2539 ± 3374	0.001
Fibrinogen	641 ± 183	660 ± 180	0.33
IL-6	34 ± 52	264 ± 111	0.001
ALT	23 ± 21	37 ± 51	0.001
AST	40.6 ± 34.32	37.9 ± 23.1	???
Albumin	3.8 ± 0.6	3.4 ± 0.4	???
Cytokine storm (% of total)	25	51	0.001
4-C score	8 ± 20	12 ± 3	0.001
SOFA score	1.3 ± 1.4	2.7 ± 2.2	0.001
O_2 supplement on admission %	55	100	0.001
High flow use (% of total)	14	82	0.001

Table 1. *Cont.*

Variable	Survivors	Non-Survivors	*p*-Value
Mechanical ventilation (% of total)	2	46	0.001
ARDS (% of total)	17	34	0.006
O_2 supply at day 7 (% of total)	18	99	0.001
Hospitalization length	9.5 ± 10	17.2 ± 13	0.001
Time to negative PCR	17 ± 8	20 ± 8	0.16
Treatment in hospitalization			
Steroid therapy (% of total)	93	97	0.26
Methylprednisolone	86	90	0.75
Dexamethasone	14	10	0.75
LMWH (% of total)	96	99	0.34
Remdesivir (% of total)	12	19	0.21
Vitamin D (% of total)	97	97	0.9

BMI: Body Mass Index, IL-6: Interleukin 6, ALT: Alanine transaminase AST: Aspartate Aminotransferase, ARDS: acute respiratory distress syndrome, LMWH: low molecular weight heparin.

3.2. Correlation between Risk Factors and Mortality in COVID-19 Patients

There was a strong correlation between age, BMI and hemodialysis with mortality in COVID-19 patients in univariate and multivariate analyses, while gender, ethnicity and comorbidities (diabetes, hypertension, lung disease) were not correlated with mortality rates in these patients (Table 2).

Table 2. A: Univariate analysis of risk factor strengths in mortality prediction. B: Multi-regression analysis of risk factors.

A—Constant	Coefficient	Conf. (±)	Std. Error	T	*p*-Value
Age	0.006	0.0002	0.001	5.43	1.07×10^{-7}
Gender	−0.049	0.071	0.036	−1.36	0.17
Ethnicity	−0.047	0.071	0.03	−1.23	0.21
BMI	0.006	0.005	0.002	2.23	0.02
DM	0.047	0.088	0.044	1.5	0.29
HTN	−0.024	0.094	0.048	−0.5	0.69
Hemodialysis	0.16	0.14	0.071	2.24	0.025
Lung Diseaase	0.05	0.116	0.052	0.86	0.38
B—Constant	**Coefficient**	**Conf. (±)**	**Std. Error**	**T**	***p***
Age	0.007	0.0019	0.001	7.7	1.45×10^{-13}
BMI	0.006	0.05	0.0025	2.34	0.0195
HEmodialysis	0.176	0.137	0.0696	2.53	0.01166

BMI: Body Mass Index, DM: diabetes mellitus, HTN: hypertension. Conf. (±): confidence interval, Std. Error: Standard.

3.3. Correlation between LFTS and Mortality in COVID-19 Patients

Higher mortality rates were associated with higher fibrinogen (T 3.7) and lower AST in univariate analysis. Albumin levels were the only strong predictor of mortality in the multivariate analysis (Table 3).

Table 3. A: Univariate analysis of the correlation between liver function tests and mortality in COVID-19 patients. B: Multivariate analysis of the correlation between liver function tests and mortality in COVID-19 patients.

A—Constant	Coefficient	Conf. (±)	Std. Error	T	*p*-Value
Fibrinogen	0.996	0.519	0.263	3.782	0.0002
INR	−0.00001	0.0003	0.0001	−0.0752	0.94
Ferritin	−0.007	0.109	0.055	−0.128	0.898
IL-6	0.000017	0.00002	0.00001	1.249	0.212
ALB	0.00003	0.00005	0.00002	1.158	0.248
AST	−0.1933	0.114	0.0578	−3.338	0.001
ALT	−0.00032	0.0034	0.0017	−0.188	0.85
B—Constant	**Coefficient**	**Conf. (±)**	**Std. Error**	**T**	***p***
ALB	−0.2136	0.1097	0.0556	−3.84	0.00016

INR: International Normalized Ratio, IL-6: Interleukin 6, ALT: Alanine transaminase AST: Aspartate Aminotransferase, ALB: Albumin. Conf. (±): confidence interval, Std. Error: Standard.

3.4. Correlation between Liver Function Tests and Severity in COVID-19 Patients according to 4c Score

Higher rates of AST and fibrinogen were associated in univariate analysis with severe COVID-19, with risk ratios of 2.74 and 1.97, respectively. The same results were seen in a multivariate analysis with a risk ratio of 2.37 for fibrinogen and a risk ratio of 2.97 in severe disease with higher AST levels (Table 4).

Table 4. A: Univariate analysis of the correlation between liver function tests and severity in COVID-19 patients according to the 4c score B: Multivariate analysis of the correlation between liver function tests and severity in COVID-19 patients according to the 4c score.

A—Constant	Coefficient	Conf. (±)	Std. Error	T	*p*
Fibrinogen	0.0003	0.00035	0.00018	1.9778	0.0493
INR	−0.0063	0.1256	0.0637	−0.0997	0.9206
Ferritin	0.000007	0.00003	0.00001	0.4791	0.6323
IL-6	−0.00003	0.00006	0.00003	−1.0135	0.312
ALB	−0.0417	0.1313	0.0666	−0.6259	0.532
AST	0.0055	0.004	0.002	2.7437	0.0066
ALT	−0.002	0.0027	0.0014	−1.4586	0.1462
B—Constant	**Coefficient**	**Conf. (±)**	**Std. Error**	**T**	***p***
Fibrinogen	0.0004	0.0003	0.00017	2.3752	0.01845
AST	0.0035	0.00236	0.00119	2.9781	0.00324

INR: International Normalized Ratio, IL-6 Interleukin 6, ALT: Alanine transaminase AST: Aspartate Aminotransferase, ALB: Albumin. Conf. (±): confidence interval, Std. Error Standard.

3.5. Correlation between Kidney Function Tests and Severity in COVID-19 Patients according to the 4c Score

More severe disease was correlated with higher BUN levels in univariate analysis with a risk ratio of 8. Moreover, the same was observed in a multivariate analysis with a risk ratio of 9.56 (Table 5).

Table 5. A: Univariate analysis of the correlation between kidney function tests and severity in COVID-19 patients according to the 4c score. B: Multivariate analysis of the correlation between kidney function tests and severity in COVID-19 patients according to the 4c score.

A—Constant	Coefficient	Conf. (±)	Std. Error	T	*p*
BUN	0.0085	0.002	0.001	8.0352	1.1822×10^{-14}
Creatinine	−0.0034	0.0049	0.0025	−1.3707	0.1712
GFR	−0.00059	0.00073	0.00037	−1.5942	0.1117
B—Constant	**Coefficient**	**Conf. (±)**	**Std. Error**	**T**	***p***
BUN	0.009089	0.00186	0.00095	9.5654	1.4013×10^{-19}

BUN: blood urine nitrogen GFR glomerular filtration rate. Conf. (±) confidence interval, Std. Error Standard.

3.6. Multivariate Stepwise Regression Analysis including Liver and Kidney Functions Tests

The three strong parameters that predict mortality were BUN followed by albumin and IL-6 levels (Table 6).

Table 6. A: Univariate analysis of the between kidney function tests and severity in COVID-19 patients according to 4c score. B: Multivariate analysis of between kidney function tests and severity in COVID-19 patients according to 4c score.

Constant	Coefficient	Conf. (±)	Std. Error	T	*p*
IL-6	0.0001	0.00009	0.00004	2.1474	0.03312
ALB	−0.1297	0.1074	0.05442	−2.3838	0.01819
BUN	0.0085	0.0033	0.00167	5.0738	9.83908×10^{-7}

IL-6 Interleukin 6, ALB: Albumin. BUN Blood Urine Nitrogen. Conf. (±) confidence interval, Std. Error Standard.

3.7. Diagnostic Accuracy of the Predictors in COVID-19 Pneumonia

The predictive value of BUN, IL-6 and albumin on mortality in COVID-19 patients the number of samples was 175 survivals and 27 non-survivors, with 85% of calculation accuracy. There is good correlation between BUN, IL-6 and albumin and the disease severity and mortality in COVID-19 patients. Sensitivity, specificity, positive predictive value and negative predictive value are 88%, 55%, 84% and 64%, respectively (Table 7).

Table 7. A. Discriminant analysis: The validity (predictive power) of BUN, IL-6 and albumin on mortality in COVID-19 patients. The accuracy of the calculations is 85%. The number of samples: Predicted condition—175 survival, 53 death, and true condition 0 for survivors and 1 for non-survivors B. The sensitivity, specificity, positive predictive value and negative predictive value.

A	Actual Count	0—Survivors	1—Non-Survivors
Survivor (0)	175	148	27
Non-survivor(1)	53	19	34
B			
	Sensitivity		88%
	Specificity		55%
	Positive Predictive Value		84%
	Negative Predictive Value		64%

4. Discussion

This study indicates that liver and kidney function tests predict severity and mortality of COVID-19 patients. It shows that higher levels of BUN, IL-6 and lower levels of albumin are correlated with higher risks of mortality.

Multiple studies have reported higher BUN levels being associated with higher mortality rates [34–36]. However, the mechanism for this is yet to be fully elucidated. The primary cellular receptor of SARS-CoV-2 is angiotensin-converting enzyme 2 (ACE-2) [37]. It is highly expressed in renal endothelial cells among other sites, and might cause an interaction between the receptor and the virus, causing lower expressions of the ACE2 protein, which can result in dysregulation of the renin-angiotensin axis. This abnormal activation might lead to increased urea absorption through the tubules, which might lead to increased BUN levels [38,39]. An increase in BUN is not only due to renal dysfunction, it might also increase due to changes in the nitrogen equilibrium, catabolic state, inflammation and renal hypoperfusion due to reduced cardiac output, hypovolemia or sepsis, which were all reported to be closely associated complications in COVID-19 patients [27,40,41].

Our analysis demonstrates that albumin levels are inversely related to mortality rates. This result is consistent with multiple studies of negative prognostic factors in COVID-19 patients [42–44]. The mechanism of hypoalbuminemia is not clear. Albumin is synthesized by the liver, and its half-life is three weeks [45]. Albumin plays important roles in maintaining oncotic pressure, lipid metabolism, transporting molecules, inflammation and thrombosis and low albumin levels are considered a biomarker of poor health status and malnutrition [46,47]. Low albumin levels in COVID-19 patients are less likely to be due to lower synthesis since there is a gap between clinical symptoms and albumin's half-life [48]. It is important to emphasize that albumin levels decrease with age [49]. This in our opinion partially explains the higher rates of disease severity and worsening outcomes related to lower albumin levels. In addition, the inflammatory state of COVID-19 patients described in several studies [50–52] is responsible for the lower albumin levels, since inflammation extravagates albumin into interstitial space due to capillary permeability [48].

Higher IL-6 values were associated with mortality of COVID-19 patients which is similar to multiple reports indicating an association between IL-6 and mortality [53–56]. IL-6 is a multifunctional cytokine mainly produced by macrophages and T lymphocytes. It regulates immune cells and plays an important role in inflammation, hematological and tumoral diseases [57]. While hemostatic values contribute the treatment of infection, exacerbated production contributes to creating a cytokine storm [58–60]. This storm can be triggered by multiple factors such as infection, toxins or responses to drugs, characterized by elevated levels of pro-inflammatory cytokines, especially tumor necrosis factor (TNF), IL-6 and IL-1 [61,62]. In addition, recent studies show that the release of IL-6 and other cytokines, due to the activation of innate and adaptive immune responses, cause respiratory failure and increased vascular permeability [63]. For its important role in the pathogenesis of the severe COVID-19 disease, IL-6 was targeted as a potential treatment. In critically ill patients with COVID-19, interleukin 6 antagonists were associated with improved outcomes including survival [64].

COVID-19 has a significant impact on the coagulation system that may manifest in coagulopathy and thrombotic complications [65]. The role of fibrinogen in predicting outcomes in COVID-19 patients has yet to be decided [66]. Levels were found to be elevated in the beginning of the disease and later decreased when disseminated intravascular coagulation happened. It was reported that levels were higher in both survivors and non-survivors, but with no statistical significance, while other studies reported an association between fibrinogen elevation and poor outcome [67–69]. One study reported that higher fibrinogen levels are associated with severe disease [70]. In our study, we found that elevated fibrinogen levels upon admission were associated with disease severity but not mortality. Fibrinogen is a glycoprotein complex that is converted to fibrin by thrombin when the tissue is injured causing bleeding to stop and blood clotting [71]. One study showed higher gene expression in vitro of the procoagulant fibrinogen factor in cells infected by the virus [72]. In addition, IL-6 release promotes the activation of the coagulation cascade that also causes higher fibrinogen levels [73].

Liver dysfunction was reported in COVID-19 patients with a wide range of liver and cholestatic enzyme abnormalities [31,69,74,75]. Abnormal liver parameters, especially

ALT and AST, are also correlated with increased mortality and morbidity in COVID-19 patients [76–80]. The potential causes of liver involvement in COVID-19 are through different mechanisms. Angiotensin converting enzyme 2 receptors are found in the liver and in bile duct epithelial cells, thus providing access to the cholangiocytes and creating liver injury [81–83]. Studies have reported disruption in AST levels, which indicates a direct impairment by the virus [84]. Another potential cause of liver injury is the systemic inflammatory response because of the overproduction of inflammatory cytokines triggering the formation of the cytokine storm [58]. Moreover, a variety of medications used to treat the virus, including antipyretics, antiviral, antibiotics and steroids, are known to cause liver damage. One study noted that drug-induced liver injury (DILI) could be a cause of liver abnormalities, with others showing antivirals, such as oseltamivir ritonavir, hydroxychlroquine and remdesivir, causing hepatotoxic effects resulting in increased liver enzymes [32,85,86].

When interpreting the result of this study, several potential limitations have to be considered. As we were confined to a single center, the sample size is not large enough to show statistical power for some of the results. Importantly, there could be several confounding parameters related to our patients characteristics, which might be the underlying cause of difference in IL-6, albumin, and BUN between the survivors and non- survivors groups.

Firstly, there is a 20-year difference in the mean age of the survivors group and the non-survivors group. Therefore, there could be an age-related cause of death, or a background diagnosis explanation for the lab value differences. In this scene, age might be a confounding parameter, particularly in regards to mortality.

For example, an age-related increase in fibrinogen is a common phenomenon that is well-documented in the literature [87]. It is possible that the increased mean fibrinogen levels in the non-survivors group is at least partially related to the aging process, and not a direct indicator of COVID-19 disease progression. Similarly, and as mentioned in the discussion, serum albumin levels are known to decrease with age. This might be at least partially related to an increase in severity of disease and increased mortality, thereby obscuring the actual relation between decreased albumin and increased COVID-19 mortality. Secondly, hypertension was 35% more prevalent in the non-survivors group compared to the survivors group. Long standing hypertension is a major cause of renal damage, as demonstrated multiple times [88]. As renal damage progresses, BUN levels increase chronically, and it is possible that the increased BUN levels are partially due to previous kidney damage, caused by long standing hypertension, although creatinine levels were not different between the two groups, on admission. Another major difference in patient characteristics between the two groups was the prevalence of diabetes mellitus, which was almost double in the non-survivors compared to the survivors. Similar to hypertension as discussed, DM is also a leading cause for renal damage and decreased GFR, and increased BUN levels are part of the course of diabetic nephropathy [89,90]. Moreover, the risk of developing diabetic nephropathy among DM patients increases with age, and as mentioned, there is a remarkable difference in the mean age of the survivors and non-survivors group. Therefore, it is possible that diabetes mellitus served as another confounder in our attempt to predict disease severity based on BUN.

BMI can also serve as a confounder as it is also linked with metabolic changes that cause alterations in kidney function. There is a close connection between BMI and the ability of the kidneys to perform its physiological role. In fact, both DM and obesity have been demonstrated as risk factors for the deterioration of kidney function. Non-survivors had a higher BMI average as their baseline state. This means that the elevation in BUN seen in this group might be affected by elevated BMI. It is important to emphasize that in our study, patient's laboratory values were documented for research analysis on admission. Therefore, there was no ability to see the progression of these values as the hospitalization continued. In our opinion, this is an important limitation of the study, as changes in the discussed markers are possibly more indicative of disease progression, and could be more useful for the clinical management of COVID-19 patients in real life settings. Focusing on

marker dynamic changes as opposed to absolute values could also address the limitation of preexisting comorbidities as confounders, as discussed above [89–91].

Because plenty of time has passed since the beginning of our research, in addition to the changing of COVID-19 variant, we cannot incorporate older control adults older than 60. Instead, we tried to decrease the age effect by filtering our database and compared survival results from patients older than 60 years old and non-survivors over 60, then compared our kidney and liver enzymes again. In this age subgroup, the age difference is much lower with 71.50 ± 9.727 and 79.97 ± 9.593 in survivals and non- survivals, respectively. IL-6, BUN, fibrinogen are statistically significant between both group.

In order to demonstrate stronger evidence for the predictive value of kidney and liver markers for COVID-19 severity, further research must be carried out. Larger sample sizes will allow for better stratification of the cohort, and will enable us to better address the question of whether or not IL-6, BUN and albumin are true markers of COVID-19 severity, independent of pre-existing comorbidities and medication use, and particularly independent of age. Perhaps more importantly, future research will need to examine the dynamic change in lab values, and the trend of change compared to each patient's baseline value on admission. For these reasons, we suggest carrying out a multi-center prospective cohort study, in a scale large enough to allow stratification of the results to address the limiting confounders. In addition, in such an initiative, we suggest that liver and kidney biomarkers will be measured throughout the hospitalization period in constant intervals (e.g., on a daily basis) to enable the analysis of dynamic changes in these values, as true predictors of COVID-19 severity.

5. Conclusions

In conclusion, when estimating kidney and liver function tests in COVID-19 patients with of Jewish and Arab ethnicity, those with higher BUN, IL6 and lower albumin levels correlated with higher mortality rates. While higher fibrinogen and AST levels were in relation with the severity of the disease. Nonetheless, larger multi-center, prospective research should be performed to assess the issue comprehensively.

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Abbreviations

BUN: Blood urea nitrogen; NLR: Neutrophil to lymphocyte ratio.

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