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Research Article

Estimation of Biochemical and Hematological Markers as Predictors of Disease Severity, Multiorgan Injury, and ICU Requirement in Hospitalized COVID-19 Patients in Al-Najaf Province: A Prospective Cohort Study

Mohammed Zuheir Hassan [1], **Ammar K. Madlool**[2], **Haider Abdul-Moneem Al-Mothafer**[3] **and Ali Jabbar Radhi** [4,5*]

[1]*Department of Aesthetic and Laser Techniques, College of Health and Medical Technology, University of Alkafeel, Najaf, Iraq.*
[2]*Department of Aesthetic and Laser Techniques, College of health and medical techniques / Kufa, Al-Furat Al-Awsat Technical University, Iraq.*
[3]*Department of Anesthesia Techniques, College of health and medical techniques / Kufa, Al-Furat Al-Awsat Technical University, Iraq.*
[4]*College of Pharmacy, University of Alkafeel, Najaf, Iraq.*
[5]*ARCPMS University of AlKafeel, Najaf, Iraq.*
[*]*Corresponding author: alijebar56@gmail.com*

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Abstract

Background: COVID-19 has been shown to cause a variety of complications throughout the body and can be classified as a 'total illness' with multi-organ involvement. Determining which patients will develop life-threatening illnesses will greatly improve physicians' ability to identify high-risk individuals and institute preventive medicine. Therefore, this research aimed to determine if laboratory biomarker data collected at the time of admission can correlate with the severity of COVID-19 illness, and to develop appropriate cut-offs for predicting organ dysfunction and determining which patients will require admission to ICUs. **Methods:** A prospective observational study of 135 patients confirmed with COVID-19 via RT-PCR (90 non-severe/ 45 severe) and 45 healthy participants, measuring bloodwork/radiologic evaluations within 24 hours of hospital admission, and again on 5–7 days post-admission. A comparison of all common laboratory diagnostics to identify differences between patients of varying disease severity (by RT-PCR). Bloodwork was obtained at 24 hours post-admission, and repeated on days 5–7. Evaluating blood work parameters included: IL-6, CRP, Ferritin, ALT, AST, Troponin, CK-MB, BNP, Creatinine, D-dimer, Complete Blood Count with Neutrophil to Lymphocyte Ratio (NLR), Lactate, Bicarbonate. Data analysis utilized the Mann-Whitney U Test, ROC curve analysis, and multivariable logistic regression to calculate odds ratios (ORs). **Results:** People with often severe or critically ill experiences had more significantly raised levels of various measurements than did any other patient group examined or that of healthy control subjects ($p < 0.001$). Among these measurements were the elevations of: IL-6, CRP, ferritin, AST, ALT, troponin, BNP, D-dimer, lactate levels within all patients who were sufficiently sick or critical versus all other groups; as well, the level of bicarbonate was greatly decreased vs. the other two groups. The NLR had clearly very good predictive value for ICU beds for all patients with an area under the curve (AUC) of 0.73 (95% CI: 0.64 to 0.82) with a cut-off value of 4.5 (Sensitivity = 76%, Specificity = 68%). Patients having an AST level greater than twice the upper limit of normal (ULN) are at grossly increased risk of dying within 60 days (Odds Ratio (OR) = 34.2; $p < 0.001$). Mild elevation of troponin occurred in 12% of patients in the non-severe group and may indicate underlying myocardial injury not being clinically detected. The above findings are consistent with both D-dimer (more than 1.5 ug/mL) and ferritin (more than 800 ng/mL) being independent predictors of the critically ill population. **Conclusion:** We found that routine biochemical and haematological parameter measurements taken at the time of admission are useful as early indicators of risk in COVID-19 patients. In particular, IL-6, NLR, AST, ferritin and D-dimer were able to provide valuable predictive data regarding disease severity, organ involvement and whether there will be a need for intensive care, thereby assisting with timely and appropriate clinical decision-making and intervention.

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1. Introduction

Worldwide, over the past few years, with an estimated total of over 700 million people infected, the COVID-19 pandemic from SARS-CoV-2 has ravaged many aspects of our daily lives [1]. Originally thought to be primarily a viral respiratory illness, scientists and physicians have found that COVID-19 is systemic in nature and can directly damage multiple organ systems, including the kidneys, heart, liver, coagulation, and immune system [2, 3]. The pathophysiology of coronavirus disease is driven by an exaggerated inflammatory response or "cytokine storm" that results in damage to the vascular endothelium, formation of clotting within small vessels, and progression to multiple organ system failure in extreme instances [4, 5]. Clinical laboratories are critical in the care of patients with COVID-19. An appropriately interpreted routine blood test can provide valuable prognostic information long before there is evidence of clinical deterioration [6]. Many studies mentioned the Cytokine effect on the severity of COVID-19, one of the most important is IL-6, in response to infections and tissue damage, interleukin-6 is quickly and momentarily created. It aids in host defense by promoting immunological responses, hematopoiesis, and acute phase responses. Even though transcriptional and posttranscriptional mechanisms rigorously regulate its expression, dysregulated continuous production of IL-6 has a detrimental impact on autoimmune and chronic inflammation [7]. Depending on the situation and signaling mechanism, the pleiotropic cytokine interleukin-6 (IL-6) can have both pro-inflammatory and anti-inflammatory effects. In autoimmunity, infections, and chronic inflammation, it functions as a pro-inflammatory agent. On the other hand, it functions as an anti-inflammatory regulator, especially in acute inflammatory reactions or muscle-derived IL-6 during exercise [8, 9].

Recent studies in 2025 and 2026 have demonstrated that serial measurements of inflammatory markers (IL-6, CRP, ferritin), organ-specific enzymes (ALT, AST, troponin, creatinine), coagulation parameters (D-dimer), and hematologic indices (i.e., neutrophil/lymphocyte ratio [NLR]) are associated with disease progression and patient outcome [10–12]. Although we have an understanding of the importance of regionally and temporally specific cut-off values, these values remain elusive for emergency settings.

This study seeks to:

1. Provide a comparison of laboratory values from admissions of patients with non-severe COVID-19 compared to patients with severe and/or critical COVID-19.
2. To identify the most accurate predictive biomarkers for ICU admission and mortality.
3. Determine optimal cut-off points using ROC analysis.
4. Determine the prevalence of subclinical organ injury (cardiac, renal, and liver) in patients with mild symptoms.

2. Methods

2.1. Study design and population

The observational study of the prospectus of several medical research projects being undertaken at Al-Sader Teaching Hospital in the City of Najaf between 1 September 2024 and 31 March 2025. Institutional ethics approval was received for the research protocols according to the institutional ethics review board, and written informed consent was obtained from all participants or their legal guardians before they could participate in the studies described.

Inclusion Criteria - Patient population: ult (at least 18-years-old) patients who have a positive SARS-CoV-2 NASOPHARYNGEAL RT-PCR test; admitted to the hospital within 48 hours after the onset of symptoms. Exclusion Criteria: Preexisting chronic liver disease; preexisting chronic kidney disease stage 4 or 5; history of a myocardial infarction within three months of the study or history of any hematologic malignancy or pregnancy.

In total, 135 consecutive patients were enrolled and categorized according to WHO Clinical Progression Scale [13]. The groups created were the following:

Non-severe group (n = 90): The patients were classified as having mild to moderate disease but did not require supplemental oxygen or have to be admitted to an intensive care unit (ICU).

45 subjects met the criteria for the severe/critical group; they required supplemental O_2, non-invasive or mechanical ventilators, or they were admitted into an intensive care unit for respiratory failure or shock. We also recruited a control group of 45 healthy individuals (no symptoms; negative PCR) matched by age and sex.

2.2. Laboratory measurements

Blood sample collections in EDTA, citrate, and plain tubes on days 0, 5-7 were used to evaluate venous blood. All laboratory examinations were performed in the central clinical laboratory utilizing fully automated technology (Roche Diagnostics Cobas 6000 biochemical analyses, Sysmex XN-9000 for hematological data). A wide variety of blood biomarkers were analyzed, including inflammatory markers (IL-6 by electrochemiluminescence immunoassay, CRP, and ferritin using immunoturbidimetry). Liver function laboratory tests (ALT, AST) were analyzed using the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) method without adding pyridoxal phosphate to the sample. Cardiac biomarkers (hs-TnT, CK-MB, BNP) were also measured using electrochemiluminescence methodology. Serum creatinine was measured using an enzymatic method for testing renal function. In a subset of patients, kidney injury molecule-1 (KIM-1) and neutrophil gelatinase-associated lipocalin (NGAL), were evaluated in urine using ELISA (enzyme-linked immunoassay) assay techniques. Coagulation status was determined based on D-dimer levels using immunoturbidimetry. Complete blood count with automated differential provided the hematological parameters obtained by routine laboratory tests, and neutrophil-to-lymphocyte ratios (NLR) were calculated from the absolute number of both neutrophils and lymphocytes in the blood sample, i.e., the total number of white blood cells is based on their normal values. Finally, acid-base status was assessed by determining lactate and bicarbonate concentrations using enzymatic methods of analysis from serum samples.

2.3. Statistical analysis

Continuous variables were presented either as means ± SD or medians (IQR), depending on normality of distribution (Shapiro-Wilk). For comparing means between 3 groups ANOVA or Kruskal-Wallis and post-hoc Bonferroni tests were used. Receiver Operating Characteristic (ROC) curves were utilized to define optimal cut-off points (youden's index) for the prediction of severe/critical illness. A logistic regression model was created to obtain adjusted odds ratios (OR) and 95% CI. A 2-sided p-value <0.05 was considered to be statistically significant. All statistical analyses were completed using SPSS version 27.0 and MedCalc 22.0.

3. Results

3.1. Baseline characteristics

Table 1 summarizes the demographic and clinical characteristics of the study sample, and shows that participants with severe/critical disease had a much higher mean age than those without (68.4 years vs 52.1 years, $p < 0.001$) and also had a higher prevalence of both hypertension and diabetes. There were no statistically significant differences between the groups in terms of sex distribution.

Table 1: Baseline Characteristics of the Study Population

Characteristic	Control (n=45)	Non-severe (n=90)	Severe/critical (n=45)	p-value
Age (years, mean ± SD)	50.2 ± 12.3	52.1 ± 14.5	68.4 ± 11.2*	<0.001
Male sex (%)	48.0	52.0	58.0	0.42
Hypertension (%)	10.0	24.0	54.0*	<0.001
Diabetes mellitus (%)	6.0	18.0	40.0*	<0.001
ICU admission (%)	–	0	100	–
In-hospital mortality (%)	–	0	28.0	–

The participants' average age was significantly older in the severe/critical group (68.4 ± 11.2 years) than in the non-severe (52.1 ± 14.5 years) and control groups (50.2 ± 12.3 years) ($p < 0.001$). Male participants made up a slightly higher percentage of the severe/critical group (58.0%) than of the non-severe group (52.0%) and control group (48.0%); however, this difference was not statistically significant ($p = 0.42$). The mean ages and gender proportions of the three study groups are summarized in Table 1.

Patients who were severely or critically ill had higher rates of co-occurring medical conditions than patients who were not. The prevalence of hypertension in severe cases was 54.0% compared to 24.0% for patients who were not severe and 10.0% for controls ($p < 0.001$). Patients who were severely/critically ill also had a higher prevalence of diabetes (40.0%) than patients who were not severely ill (18.0%) and the control group (6.0%) ($p < 0.001$).

Every patient who was classified as severely/critically ill required an ICU admission (100%). No other patients classified as non-severe were admitted to the ICU. Severe/critical patients had a higher in-hospital mortality rate than did non-severe patients (28% vs. 0%), which was statistically significant ($p < 0.05$) when compared to the non-severe patient population based upon age, presence of hypertension, and diabetes.

3.2. Inflammatory markers (cytokine storm)

Severe/critical cases had significantly greater levels of IL-6, CRP, and ferritin compared to non-severe patients and control samples as can be seen in table 2 (all $p < 0.001$). The median level of IL-6 in severe patients is 85.4 pg/mL while the median level of IL-6 in non-severe patients is 12.3 pg/mL. Of all severe patients, 74% had a ferritin level > 800 ng/mL while only 12% of non-severe patients had the same measurement.

Table 2: Inflammatory markers at admission

Marker	Control	Non-severe	Severe/critical	P- value (severe vs. non-severe)
IL-6 (pg/mL), median (IQR)	2.1 (1.5–3.2)	12.3 (7.8–21.4)	85.4 (42.6–156.2)	<0.001
CRP (mg/L), median (IQR)	2.0 (1.0–3.5)	28.5 (14.2–56.3)	142.7 (89.5–210.4)	<0.001
Ferritin (ng/mL), median (IQR)	85 (45–142)	342 (210–580)	1240 (820–2150)	<0.001

3.3. Organ damage markers

Liver function

High levels of ALT and AST were frequently detected in serious cases. There were 62%, of all severe cases, whose AST levels were more than double the ULN with regard to the predictor of death, (OR = 34.2, 95% CI: 8.7–134.5, $p < 0.001$).

Cardiac markers

A total of 92% of severely infected HS-troponin T patients had elevated HS-troponin T (>14 ng/L) compared to 12% of non-severe HS-troponin T patients, demonstrating subclinical evidence of myocardial injury in mild disease as demonstrated by BNP levels being significantly greater in those with severe disease (median 345 pg/mL vs 86 pg/mL $p < 0.001$).

Renal function

Forty-four percent of severe patients had elevated creatinine levels upon admission, while a further twenty-eight percent developed acute kidney injury (AKI) during their hospital stay. Of the thirty severe patients studied using urinary NGAL and KIM-1, strong correlations exist between each biomarker and the patient's need for renal replacement therapy (NGAL area under the curve = 0.89).

Table 3: Organ damage markers at admission (median, IQR)

Marker	Control	Non-severe	Severe/critical	P
ALT (U/L)	22 (18–28)	35 (26–58)	82 (52–146)	<0.001
AST (U/L)	24 (20–30)	42 (30–68)	118 (74–210)	<0.001
hs-TnT (ng/L)	5 (3–8)	10 (6–18)	42 (22–86)	<0.001
BNP (pg/mL)	25 (15–42)	86 (45–142)	345 (189–620)	<0.001
Creatinine (mg/dL)	0.8 (0.7–0.9)	0.9 (0.7–1.1)	1.4 (0.9–2.3)	<0.001

3.4. Coagulation and hematology parameters

The results showed significant differences between the two groups. For example, the level of D-dimer is much higher in the group with severe disease (median value = 2.8 µg/mL) than in those without severe disease (median value = 0.6 µg/mL), $p<0.001$). In addition, the neutrophil/lymphocyte ratio (NLR) was most effective at differentiating between patients with/without severe disease as evidenced by the greater median NLR for severe versus non-severe patients (7.8 vs. 2.9, $p<0.001$).

Table 4: Coagulation and hematological markers

Marker	Control	Non-severe	Severe/critical	P
D-dimer (µg/mL)	0.2 (0.1–0.3)	0.6 (0.4–1.0)	2.8 (1.5–5.2)	<0.001
Neutrophils ($\times 10^9$/L)	3.8 (2.9–4.5)	5.2 (3.8–7.1)	9.6 (7.2–13.4)	<0.001
Lymphocytes ($\times 10^9$/L)	2.1 (1.6–2.5)	1.4 (1.0–1.9)	0.8 (0.5–1.2)	<0.001
NLR	1.8 (1.4–2.3)	3.7 (2.4–5.6)	12.0 (7.8–18.5)	<0.001

3.5. Acid-base balance

The findings show that lactate levels are significantly increased while levels of bicarbonate are significantly decreased in patients with severe metabolic acidosis, which is consistent with tissue hypoperfusion and tissue hypoxia. Lactate concentrations are incrementally increasing among groups, with the most notable differences being between control (lactate = 1.2 [0.9-1.6] mmol/L) and severe and critical illnesses (lactate = 3.5 [2.6-5.1] mmol/L) ($p < 0.001$). However, bicarbonate concentrations are continuously decreasing between control (bicarbonate = 24.5 [23-26] mmol/L), non-severe (bicarbonate = 23.1 [21-25] mmol/L), and severe (bicarbonate = 18.2 [15-21] mmol/L) ($p < 0.001$).

3.6. ROC analysis and cut-off values

The ROC curves were developed to determine the best predictors with respect to the diagnosis of severe/critical disease (ICU admission). The results are summarized in Table 5, NLR had an AUC of 0.73 (95% CI: 0.64-0.82), the sensitivity at a cut-off of > 4.5 was 76% and the specificity was 68%. Ferritin > 800 ng/mL had an AUC of 0.78, and D-dimer > 1.5 µg/mL had an AUC of 0.74.

Table 5: Diagnostic accuracy of selected biomarkers for predicting severe/critical disease

Biomarker	Cut-off	AUC (95% CI)	Sensitivity (%)	Specificity (%)
NLR	>4.5	0.73 (0.64–0.82)	76	68
Ferritin	>800 ng/mL	0.78 (0.69–0.86)	74	82
D-dimer	>1.5 µg/mL	0.74 (0.65–0.83)	70	75
IL-6	>35 pg/mL	0.81 (0.73–0.89)	82	78
AST	>2× ULN	0.70 (0.60–0.80)	62	85

3.7. Multivariate logistic regression

After aged, sex, and comorbidity considerations were adjusted, ferritin levels over 800 ng/mL (OR=5.2, p=0.001), D-dimer levels over 1.5 µg/mL (OR=4.1, p=0.003), NLR exceed 4.5 (OR=3.6, p=0.008), and IL-6 concentration greater than 35 pg/mL were independent predictors for determining the likelihood of being admitted to the Intensive Care Unit. According to our results, AST amounts greater than twice the upper limit of normal were the most significant predictor of mortality with an OR of 34.2 ($p<0.001$).

4. Discussion

A prospective investigation of 135 patients with COVID-19 and 45 healthy controls supports the ability to use a panel of easily obtainable biochemical and hematological values, obtained upon admission to hospitals, to categorize patients according to disease severity and predict likely organ complications. The most noteworthy findings included: patients with severe or critical disease have a significant cytokine storm, where levels of IL-6, CRP, and ferritin are very high; liver, cardiac, and renal injury markers are frequently elevated in severe disease; the neutrophil-to-lymphocyte ratio (NLR) is a simple, inexpensive, valid predictor of admission to the intensive care unit (ICU); elevations of D-dimer are strongly associated with thrombotic events and poor outcomes; and subclinical cardiac injury occurs in significant percentages of mild cases (e.g., with troponin elevations to a minimal level).

According to previous studies, the data we analyzed support findings reported in these recent studies. A large multi-center studies found that a ferritin level greater than 3 times of the reference values and more, has an independent increased risk of severe disease [14–16]. In our study, we also validated the NLR as an accurate prognostic indicator of outcome from COVID-19; our AUC of 0.73 is analogous to that reported in other studies [17, 18]. The very high odds ratio for mortality associated with elevated AST > 2 ULN (HR=34.7, $p < 0.001$) emphasizes the importance of liver dysfunction as a prognostic indicator of severity of disease, possibly due to an overall inflammatory response rather than solely from the direct effect of the virus on liver tissue [19].

An interesting observation from this study was that 12% of patients without severe symptoms had a troponin level greater than the upper limit of the normal range (ULN), even though they reported no cardiac symptoms. This supports the notion that SARS-CoV-2 is associated with subclinical vascular injury in mild disease, as demonstrated by recent proteomic studies [20]. There may be a group of patients in this cohort who would benefit from enhanced monitoring and potentially receive early anti-inflammatory and/or anticoagulant treatment.

Cytokine storm has an important place in the pathophysiology associated with severe COVID - 19 disease. In this study, IL - 6 levels were highest in critical patients, correlating with IL - 6's role as a therapeutic target (eg. tocilizumab). However, IL - 6 assays are not routinely performed in resource - limited settings; thus, alternative biomarkers (ferritin and CRP) may be used as cost - effective alternatives with acceptable predictive value (AUC 0.78 and AUC 0.72) and our study in compatible with the previous studies [21–23].

The prediction of AKI progression was significantly enhanced by the urinary biomarkers (KIM-1 & NGAL). While these tests aren't typically conducted as routine tests, they should be considered for high-risk patients who may eventually require some form of renal replacement therapy [24].

4.1. Clinical implications

The present study found evidence to support the use of a lab-based risk score at the time of admission based on a combination of NLR, ferritin, D-dimer, and AST. Patients who have an NLR greater than 4.5; ferritin greater than 800 ng/mL; and D-dimer greater than 1.5 µg/mL may warrant early referral to ICU, more aggressive anti-inflammatory treatments, and anticoagulation therapy. The presence of an AST greater than two times the ULN may indicate an increased risk of mortality.

4.2. Limitations

This research has a number of limitations. One limitation is that it was done in a single center and only used a moderate sample size. Another limitation is that we did not measure any viral load, nor did we do repeat cytokine profiling after day seven. A third limitation was that the longitudinal follow-up of the control group was not done. Finally, the fourth limitation is that there were only a small number of subjects who provided urine and those analyses will again be hurt statistically due to small sample size. Therefore, validation of these proposed cut-off values will require larger, multi-site prospective studies.

5. Conclusion

Biochemical and hematological measurements, such as the NLR, ferritin, d-dimer, AST, and troponin, may serve as prognostic markers of how severe the disease course of COVID-19 is, how severe the disease is affecting the body, and if there are organ-related complications. As such, even if troponin levels are only modestly elevated in a non-severely ill patient, this should indicate that the patient is experiencing some level of subclinical cardiovascular pathology. In this regard, having access to the above parameters at the time of the admission panel can assist the process of triage, help with optimizing resource allocation, and improve clinical outcomes. Moreover, the levels of IL-6 are very high in ICU-admitted patients than in non-severe patients and the healthy group. Because of its low cost and widespread availability, the NLR should be utilized more frequently as a first-line tool for risk assessment, compared to other existing tools.

Article Information

Disclaimer (Artificial Intelligence): The author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.), and text-to-image generators have been used during writing or editing of manuscripts.

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