Laboratory parameters as predictors of clinical outcome in hospitalized COVID-19 patients

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Key words: Covid-19, laboratory predictors, death

Abstract

Background This study aims to describe reliable laboratory parameters that could be used as predictors of severity in hospitalized COVID-19 patients. **Methods** This is a retrospective cohort study using anonymized data from clinical records of patients from two COVID-19 isolation centers at Aliaa specialized hospital and Universal hospital in Khartoum State, Sudan, between Feb 2020 and July 2021. The outcomes of interest were death or discharge. The study population was divided into survivors n=197; 48.5%) and non-survivors (n=169; 41.6%). In addition, two laboratory results were recorded, the first on the day of admission and the last before discharge or death. **Results** Non-survivors displayed significantly higher values of white blood count (WBC), C-reactive protein (CRP), urea, and sodium, as well as decreased haemoglobin levels, lymphocytes-and platelets. In multiple regression analysis, WBC, CRP, urea, haemoglobin, lymphocytes, platelets and advanced age remained significant predictors of in-hospital death. Sinus Tachycardia (>100Bpm) found to be a strong predictor for mortality OR 5.925(95%CI. 2.853-12.31) P=0.000The most common complications found to be associated with increased mortality among Covid 19 cohorts were Septic Shock OR 3.640(95% CI (1.497-8.852), Acute kidney injury OR 2.836 (95%CI 1.561-5.154), Type II Respiratory failure OR 2.068 (95% CI

 online ISSN 1858-6279 ISSN 1858-6155

1.042-4.102) and Type I Respiratory failure OR 2.931 (95%CI 1.102-7.792) p<0.05 for all cases. **Conclusions** This study highlighted the most important laboratory abnormalities in a subset of Sudanese COVID-19 patients that are highly predictive of in-hospital mortality. Considering these parameters during the management of COVID-19 patients may improve the outcome of the disease.

Introduction

In early December 2019, Coronavirus disease (COVID-19), caused by severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2), first emerged in Wuhan, China. By May 2020, over four million COVID-19 cases and 280,000 deaths had been reported globally, reflecting the high virus transmission rates.[1] COVID-19 is not a localized respiratory infection but a multisystem disease caused by a diffuse systemic process involving a complex interplay of immunological, inflammatory and coagulative cascades.[2] The significant variations in the clinical features of the disease, spanning from asymptomatic to fatal, necessitate the identification and application of reliable laboratory biomarkers.[3] Reliable biomarkers are needed to identify patients who will suffer rapid disease progression to severe complications and death and may be helpful for screening, clinical management, and prevention of serious complications.[4]

The main routine tests requested for COVID-19 patients include a complete blood count (CBC), coagulation, fibrinolysis, and inflammatory-related parameters (ESR, CRP, ferritin, and procalcitonin). In addition, biochemical analysis is crucial for clinicians to evaluate the functional activities of vital organs such as the heart, liver, and kidneys due to the virus's potential ability to damage these organs. Therefore, this study aimed to retrospectively investigate the changes in hematological and biochemical routine laboratory parameters in adult Sudanese patients with COVID-19 to identify predictors of clinical outcomes in this population.

Material and Methods:

Ethical approval:

The study was approved by the Ethical Committee of the Federal Ministry of Health. All collected data was anonymized to guarantee patient privacy.

 online ISSN 1858-6279 ISSN 1858-6155

Study design and Population

This is a retrospective cohort study using anonymized data retrieved from clinical records of patients from two COVID-19 isolation centers at Aliaa specialized hospital and Universal hospital in Khartoum State, Sudan.

We included the records of all patients with laboratory-confirmed COVID-19 disease hospitalized in the two isolation centers between Feb 2020 and July 2021**.** Data included demographic data, presenting symptoms, disease complications**,** hematological profile, biochemical markers, coagulation profile and arterial blood gas measures**.**

The outcomes of interest were death or discharge from the hospital Study population was divided into survivors (or discharged; n=197; 48.5%) and non-survivors (n=169; 41.6%). Two laboratory results were recorded, the first on the day of admission and the last before discharge or death

Statistical analysis:

All Statiscal analysis were performed using SPSS 26 (SPSS Inc., Chicago, IL)

Demographic, clinical and laboratory were undertaken using chi square test for proportions (with Monte Carlo correction in case of small sample sizes), and 2-sample *t* test or non-parametric continuous variables, appropriate. A multi-logistic regression model was used to determine the predictive value of the laboratory biomarkers for mortality in COVID-19 patients. The level of significance was $p \leq 0.05$.

Results

Demographic characteristics of patients with COVID-19

Table 1 shows the basic characteristics of the study cohort segregated by outcome (survivors versus non-survivors). A total of 406 patients hospitalized with COVID-19 were included in the Study (71.0% males and 29% females). The mean age in years among non-survivors was significantly higher than survivors (67.0 ±13.1 vs. 62.5±13.1) ($p<0.001$). Among our study cohort, 44.8% were admitted to the ICU, and the mortality rate was 46%.

The non-survivor cohort has lower mean diastolic blood pressure (DBP) and elevated

 online ISSN 1858-6279 ISSN 1858-6155

Resting heart rate (RHR) compared to survivors (p<0.05). Regarding disease complications, non-survivors were more likely to develop septic shock (75.9%), type2 respiratory failure (71.4%), acute kidney injury (69.2%) and type I respiratory failure (58.2%) (p<0.005) in all cases.

Initial and final laboratory test results among Survivors and non- Survivors

The patients' initial and final laboratory results are presented in Table 2. Two laboratory investigation sets of results were analyzed; the first investigations were requested at admission, while the second was ordered just before discharge or death. No significant difference in the laboratory parameters was observed between survivors and non-survivors at admission except for CRP. Increased levels of WBC, CRP, urea, and sodium, as well as decreased levels of hemoglobin, lymphocytes-and platelets, were observed among non - survivors (p<0.05).

Predictors of COVID-19 disease outcome

Table 3 shows the multilogistic regression analysis performed to identify risk factors associated with in-hospital mortality. Using a *p*-value ≤ 0.05, as the cut-off for inclusion criteria, after adjusting for age, gender, and comorbidities.

After adjusting for other covariates, the odds of mortality were twice higher among patients older than 65 years. OR = 2.132 (95%CI 1.31-3.38), p-*value = 0.002*). Sinus Tachycardia (>100Bpm) was found to be a strong predictor for mortality in Covid 19 patients, as the risk of mortality increased more than five times OR 5.925(95%CI. 2.853-12.31) P=0.000

Regarding laboratory markers, strong predictors of mortality included raised WBC, CRP, and urea levels as well as decreased hemoglobin, lymphocytes-and platelets (p<0.05).

Septic Shock, Acute kidney injury, Type II RF and Type I RF were associated with increased mortality among Covid 19 cohorts P<0.05.

 online ISSN 1858-6279 ISSN 1858-6155

Table 1: Demographic characteristics of patients with COVID-19

Characteristics	**Total Patients N=406**	**Survivors 54%**	**Non-Survivors 46%**	**p-value**
Age (mean ±)	65.0 ± 13.5	62.5 ± 13.1	67.0 ± 13.1	0.001
Gender, Male (%)	71.0 %	54.4 %	45.6 %	0.77
Hypertensives %	60.0 %	52.3 %	47.7 %	0.46
Diabetics %	48.0 %	50.3 %	49.7 %	0.20
Initial SBP (mean ±SD)	139 ±24	140 ±25.0	138 ±24.0	0.37
Initial DBP (mean ±SD)	78 ± 15.4	80 ±18.1	76 ±14.4	0.03
Initial RHR (mean ±SD)	92 ±16.8	89 ±15.5	94 ±17.5	0.01
Complications				
Type IRF	36.7 %	41.8 %	58.2 %	0.023
AKI	17.8 %	30.8 %	69.2 %	0.000
Septic Shock	7.9 %	24.1 %	75.9 %	0.001
Type II RF	5.8 %	28.6 %	71.4 %	0.017
ICU admission	**44.8 %**	**19.2 %**	**24.0 %**	**0.964**

 online ISSN 1858-6279 ISSN 1858-6155

Key: SBP=Systolic Blood pressure; DBP=diastolic blood pressure; RHR=resting heart rate; Type IRF=Type I respiratory Failure; AKI= Acute kidney injury; TypeII RF= Type II respiratory failure

Table2: Laboratory results of patients with COVID-19

Blood routine	**Normal value**	**First Readings**			**Last reading**		
		Survivors N=197	**Non-Survivors N=169**	**p-value**	**Survivors N=197**	**Non-Survivors N=169**	**p-value**
		Mean ±SD	**Mean ±SD**		**Mean ±SD**	**Mean ±SD**	
WBC	4.0–11.0 x10 ^{3}/ µ	10.8±5.9	10.7±5.8	0.878	12.7±9.1	16.2±8.4	**0.001**
Lymphocyte %	20–40 %	11.1±9.0	10.4±6.8	0.515	15.1±8.7	9.6±4.9	**0.037**
Platelets	150 -450·/10^{9}	268± 116.1	240± 97.0	0.088	261±130.1	198±111.2	**0.001**
Hemoglobin	13.5–15·0 g/L	12.2±2.0	12.3±1.7	0.761	11.5±2.2	10.6±1.9	**0.005**
Dimer	< 500 ng/ml	2668±3065	3176±3650	0.459	3828±3690	4064±2469	0.811
Prothrombin Time	12-14	20.4±6.7	21.2±6.6	0.591	27.2±8.0	26.2±7.1	0.631
C-reactive protein	0·0–6·0 mg/L	138±100.1	172±94.2	**0.047**	97±74.1	141±97.0	**0.016**
BUN	10–50 mg/dL	61.6± 45.0	70.6±60.0	0.214	73.2±56.0	89.0±49.5	**0.054**
Serum Creatinine	0.57–1.1 mg/dL	2.1±1.8	1.9±1.3	0.578	2.0±1.6	2.1±1.8	0.748
ALT	10.0–35·0 U/L	42.2± 39.4	39.6±23.4	0.427	63.6± 55.2	57.0± 33.1	0.975
AST	10·0–35·0 U/L	64.5±46.4	56.5±52.1	0.192	91.2±57.1	93.3±52.2	0.83
Direct Bilirubin	0.0-0.25 mg/dl	0.36±0.21	0.25±0.16	0.190	0.42±0.56	0.44± 0.47	0.875

 online ISSN 1858-6279 ISSN 1858-6155

Total Bilirubin	0.0-1.1 mg/dl	0.53±0.25	0.47±0.19	0.555	0.61±0.34	0.84±0.42	0.376
Albumin	3.5–5.5 g/dL	2.87±0.60	2.97±1.57	0.663	2.2±0.67	2.36±1.6	0.354
R B G	≤ 140 mg/dL	205.5±100.2	207.4±95.1	0.878	183.7±71.7	205.0±88.4	0.151
Serum Sodium	135–145 mEq/L	135.3±5.7	137.0±7.9	0.054	138.0±6.2	140.0±7.3	**0.039**
Serum Potassium	3.6-5.2 mmol/L	3.9±0.69	4.0±0.76	0.251	4.0±0.72	4.1±0.83	0.326
Serum Calcium	8.6-10.2 mg/dL	9.0±1.2	13.2±2.3	0.378	8.5±1.1	8.1±1.0	0.463

Key: WBC= White blood cells; BUN= blood urea nitrogen; ALT= Alanine transaminase; AST= Aspartate transaminase; RBG= random blood glucose

Table 3: Logistic Regression Analysis for Risk factors Associated with in-hospital death among COVID-19 patients

Characteristics	**p-value**	**OR (95%CI)**
Age	0.002	2.132 (1.31-3.38)
Gender	0.75	1.101 (0.69-1.78)
HTN	0.951	0.951 (0.60-1.40)
DM	0.291	1.261 (0.81-1.95)
DBP	0.992	1.004 (.0482 -2.08)
RHR	0.000	5.925 (2.853 – 12.31)
WBC	0.002	2.792 (1.47-5.27)
Lymphocytes%	0.026	0.210 (0.053 -0.83)
Platelets	0.009	0.397 (0.200 -0.79)
Hb	0.052	0.342 (0.114-1.022)

 online ISSN 1858-6279 ISSN 1858-6155

CRP	0.013	2.738 (1.23-6.075)
Creatinine	0.060	1.856 (0.973-3.542)
Urea	0.004	3.011 (1.422-6.378)
Na	0.931	1.555 (0.800-3.023)
Complications		
Septic Shock	0.004	3.640 (1.497 -8.852)
AKI	0.001	2.836 (1.561-5.154)
Type IRF	0.038	2.068 (1.042 -4.102)
Type II RF	0.031	2.931 (1.102-7.795)

Key: HTN= hypertension; DM= Diabetes mellitus; DBP= diastolic blood pressure; RHR = resting heart rate; WBC= white blood cells; Hb= Hemoglobin; CRP = C - reactive protein; Failure; AKI= Acute kidney injury; Type IRF=Type I respiratory TypeII RF= Type II respiratory failure

Discussion

Our study investigated reliable laboratory parameters which could be used as predictors of severity in hospitalized COVID-19 patients. Identifying such parameters is needed considering the limited healthcare facilities and recourses in economically compromised countries, especially when facing a massive number of patients during the pandemic.

Two laboratory investigation sets of results were analyzed; the first investigations were requested at admission, while the second was ordered just before discharge or death. No significant difference in laboratory parameters was observed between survivors and non-survivors at admission except for CRP**.** However, increased levels of WBC, CRP, and urea, as well as decreased levels of hemoglobin, lymphocytes-and platelets, were observed among non-survivors and were found to be associated with severe sequelae of COVID-19.Elevated CRP and WBC count are considered sensitive systemic, acute-phase inflammatory mediators that play a vital role in diagnoses, prognosis and severity of Inflammation.[(5)]These laboratory parameters reflect the possible presence of viremia and bacterial co-

 online ISSN 1858-6279 ISSN 1858-6155

infection.[6] According to our results, CRP value and WBC count were significantly higher among non-survivors. This is vital since elevated CRP and WBC are related to the release of pro-inflammatory cytokines and play a role in the phenomenon of cytokine storm strongly related to the pathogenesis and severity of COVID-19. [7]

In our Covid 19 patients, a substantial decrease in the total number of *lymphocytes* was detected among non-survivors. Lymphopenia could be attributed to the effect of SARS-CoV-2, as viral replication on T lymphocytes causes its depletion and consequentially inhibits the body's cellular immune response. [8]

A remarkable drop in platelets count was detected among the non-survivors cohort during the hospitalization period, and this may be related to the host-virus interaction**.** [9] As severe viral infection causes endothelial injury that triggers thrombocyte activation and aggregation**,** leading to platelets depletion, apoptosis, and microthrombi formation. [10]

Low hemoglobin levels and anaemia were associated with poor prognosis and mortality among COVID-19 patients, as the increased oxygen demands of the peripheral tissues due to hyper metabolic state during infection may aggravate the severity of viral infection. [11]

The mean level of hemoglobin on admission was slightly below normal levels. A significantly lower level was observed in the non-survivors compared to the survivors' cohort. Although the level of hemoglobin was not decreased to an anaemic level, further investigations are required to justify the association of the reduced hemoglobin level with the poor outcome of Covid 19 patients. The markedly high urea level among non-survivors was associated with the lethal outcome of the disease. This might be attributed to reduced angiotensin-converting enzyme 2 (ACE2) expressions in the kidney following SARS2 infection. This lead to abnormal activation of the renin-angiotensin-aldosterone system (RAAS). [12] The activated RAAS can significantly increase water absorption by kidney tubules and enhance the resorption of urea, leading to elevated BUN levels. Elevated BUN reflects the inflammatory status, nitrogen imbalance, sepsis, renal hypoperfusion, and hypovolemia. [13]

Advanced age increases the risk of mortality. It has been reported that a 10% increase in mortality rate was estimated every year after the age of 30 years. This is mainly attributed to increased susceptibility to infection, chronic diseases and decreased immunity in the elderly**.** [14]

Saha SA reported sinus tachycardia in Covid 19 patients might be due to fever, systemic Inflammation, shortness of breath, hypoxia, and dehydration. [15] Our results showed that Sinus tachycardia is significantly associated with COVID-19 patients' mortality (OR 5.925(95%CI. 2.853-12.31). Sinus

tachycardia seems to be a warning sign for death as it causes heart ischemia, decreased cardiac output, cardiomyopathy, and cardiac arrest. **(16)**

Severely ill Covid 19 patients were found to be more susceptible to developing septic shock, as they are more prone to bacterial and fungi co-infection in addition to the development of drug resistance. **(17)** Septic shock was the most prevalent complication in our study cohort. Patients who developed septic shock were 3.6 times more likely to die due to COVID-19. To prevent infection and reduce the risk of in-hospital mortality, antibiotics have been added to the Covid 19 management protocol.

In conclusion,

Increased WBC, CRP, urea and decreased lymphocyte, hemoglobin and platelet levels during hospitalization are significant predictors of in-hospital mortality. Considering these parameters during the management of COVID-19 patients may improve the outcome of the disease.

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Misdiagnosis of Ewing's sarcoma, A tragedy of a young female initially diagnosed with chronic osteomyelitis and ended with disarticulation (Case report)

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