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Laboratory Markers Versus Ct Severity Score In Predicting Mortality In Covid 19

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Abstract

Aim: Predicting the mortality of COVID-19 with a spectrum of complications is a difficult task for prognostication and management. When individual level data of COVID-19 patients were not yet available, there is a need for risk predictors to support the treatment decisions. The study aims to identify the high accurate marker to measure the prognosis and outcome of COVID19.

Methods:

COVID-19 course is divided into four stages, according to chest computed tomography (C.T.) progress. The demographics, disease exposure history, clinical condition, laboratory tests, computed tomographic chest scan, and outcome data were collected and measured their correlation to assess the risk predictor.

Results:

The 10.4% mortality (n=52) was observed in total population. D-dimer (µg/dL) levels observed as 0.75 ± 0.65 in expired patients. NLR ratio observed as 17.1 in expired patients. Ferritin levels were observed as 49.8 ± 32.5 in expired patients. A D-dimer positive predictive value of 72.5% and a negative predictive value of 88% for a predictor of mortality. Ferritin positive predictive value of 35.5% and a negative predictive value of 76.5% for the predictor of mortality. Hence, the AUC of serum ferritin 0.598 represents the poor ability to discriminate the prediction for the cause of death than D-dimer levels. D-dimer > 2 µg/dL on admission was associated with in-hospital death. These main findings indicate that D-dimer on admission >2.0 µg/dl was the independent predictor of hospital death in patients with Covid-19. A D-dimer has the highest positive predictive value than serum ferritin levels.

Conclusion: The AUC for D- dimer at admission was 0.880, with an optimal cutoff of 2.2 µg/dL in predicting the cause of mortality. D-dimer on admission > 2.0 µg/mL (fourfold increase) is the best predict in-hospital mortality and a helpful marker to improve the management of Covid-19.

Keywords: severe acute respiratory syndrome, COVID19, D-dimer, ferritin, CT score

1. INTRODUCTION

The severe acute respiratory syndrome (SARS) and the Middle East respiratory syndrome (MERS) outbreaks have garnered public health emergencies in 2002 and 2012. At the end of 2019, an epidemic of pneumonia without known etiology was reported in China, with more than 11 million people [1]. 2019-nCoV is an emerging virus belonging to the Coronaviridae family, presumably derived from a bat animal SARS-like coronavirus and transmitted to humans after the emergence of mutations in the protein S nucleocapsid N protein. According to WHO, COVID-19 has already spread globally with 8,900,000 diagnosed cases in 210 countries, causing 465,000 deaths as of June 20, 2020[2, 3].
COVID-19 is a respiratory syndrome with symptoms of dry cough, dyspnea, and fever (8–15% based on the individual) result in a critical condition requiring specialized management at ICU [4]. Early detection of the risk of severe complications of COVID-19 is of clinical importance. The various study reports show that the prevalence of severe COVID-19 was 15.7 - 26.1% in total hospital admission, and these cases were associated with abnormal chest C.T findings and laboratory data. Most studies have discussed the clinical features and imaging findings of COVID-19, few studies have addressed the diagnostic and prognostic value of abnormal laboratory findings [5]. Covid-19 was associated with hemostatic abnormalities and markedly elevated D-dimer levels and serum ferritin levels in expired patients [6]. The prognosis value and the optimal cutoff for D-dimer and ferritin levels during the admission to predict mortality have not been well evaluated.
To better represent how abnormal laboratory findings are essential in COVID-19 diagnosis and prognosis, we studied laboratory parameters and their association in diagnosed 500 patients with COVID-19 infection.
Rationale:
After its first description, COVID-19 attracted attention in a short period, and the number grows unceasingly. The role of laboratory assessments to screen COVID-19 has not yet been standardized.

2. MATERIALS AND METHODS:

A retrospective study of the records of 500 patients was performed for patients with positive testing for SARS-CoV-2 using any of the platforms. The demographics, disease exposure history, symptoms, laboratory tests, chest C.T scan, and outcome were collected—laboratory tests including D-dimer, ferritin, and complete blood count.
We used univariate significance analyses of the differences in continuous features between alive and deceased patients using the Student's t-test and categorical features using the chi2 test. The positive predictive and negative predictive values of ferritin levels for each outcome of interest across all ferritin and D-dimer cutoffs were calculated. We calculated the area under the curve to evaluate admission accuracy and maximum ferritins in predicting the outcome. A P-value of 0·05 was considered as significant in this study.
Results:
According to C.T chest findings, COVID-19 was categorized into four stages: initial, progression, peak, and the recovery stage. The mean duration of follow-up was 20.8 ± 19.9 days, with a range of 1-108 days. The mean age of 55.8 ± 20.2 years with no difference between the discharged and deceased patients (P = 0.65).
The mean ferritin on admission and the maximum value of 318.23 ng/ mL and >2000 ng/mL, respectively. A ferritin of >500 ng/mL on presentation was seen in 105 patients (21%), and 395 patients (79%) had a maximum ferritin ≤ 500 ng/mL over their hospital stay. Only 5 patients (0.2%) had a ferritin >2000 ng/mL on presentation at admission. The mean

presentation and maximum ferritins were significantly different in patients who live and expired for COVID-19 (P < 0.001). As detailed in Table 1, of the 52 patients who did not survive, the mean presentation ferritin was 727.14 ng/mL, and the mean maximum ferritin was >2000 ng/mL. For the 448 patients who survived, the median presentation ferritin was 271 ng/mL. Ferritin (µg/L) levels were observed as 42.5± 28.5 in discharged patients. Ferritin levels were observed as 49.8 ± 32.5 in expired patients. However, the association does not show statistical significance (P=0.21).

The mean D-dimer (µg/dL) at admission was 0.845 and of the maximum value over admission was 18.4 µg/dL respectively. A D-dimer of ≤ 0.14 µg/dL on presentation was seen in 187 patients (37.4%), and 313 patients (62.6%) had D-dimer > 0.14 µg/dL at admission. D-dimer (µg/dL) levels observed as 0.21 ± 0.32 in discharged patients. D-dimer (µg/dL) levels observed as 0.75 ± 0.65 in expired patients. The association showed statistical significant (P< 0.001) (Figure 1).

The NLR ratio was observed as 6.03166 in discharged patients. NLR ratio observed as 17.1 in expired patients. The association does not show statistical significance (P=0.07).

The mean length of stay at the hospital was 21.8 days for discharge patients and 12.1 days for expired patients. The association shows a significant difference.

Receiver operator curve:

The AUC for ferritin at admission was 0.598, with an optimal cutoff of 727 ng/mL in predicting the cause of mortality. A ferritin positive predictive value of 35.5% and a negative predictive value of 76.5% for the predictor of mortality. The AUC for ferritin was 0.598, with an optimal cutoff of 727 ng/mL to predict mortality (Table 2).

The AUC for D- dimer at admission was 0.880, with an optimal cutoff of 2.2 µg/dL in predicting the cause of mortality. A D- dimer positive predictive value of 72.5% and a negative predictive value of 88% for the predictor of mortality. The AUC for maximum D-dimer was 0.880, with an optimal cutoff of 2.2 µg/dL in predicting the mortality.

Hence, the AUC of serum ferritin 0.598 represents the poor ability to discriminate the prediction for the cause of death than D-dimer levels.

Table 1. Statistical analysis of laboratory parameters.

Group Statistics					
	OUTCOME	N	Mean/median/percentage	Std. Deviation	P-value
AGE	Discharge	448	53.2058	14.1227	0.11(ns)
	Death	52	64.80769	11.26166	
CT SCORE	Discharge	448	28/40	10/40	0.85 (ns)
	Death	52	27/40	9/40	
D-DIMER	Discharge	448	0.687772277	1.63497596	<0.001**
	Death	52	2.193617	2.726746	
S.FERRITIN	Discharge	448	271.268198	287.916289	<0.001**
	Death	52	727.1465	474.0459	
NLR	Discharge	448	6.03166	-	0.07(ns)
	Death	52	17.12692	-	
LOS	Discharge	448	21.81879195	20.47903457	0.025*
	Death	52	12.11538	11.94539	
Gender	Male-death	N=41	-	-	chi-square =2.4385; P=0.118389
	Female-death	N=11	-	-	

Gender	Male-discharge	N=306	-	-	(ns)
	Female-discharge	N=142	-	-	

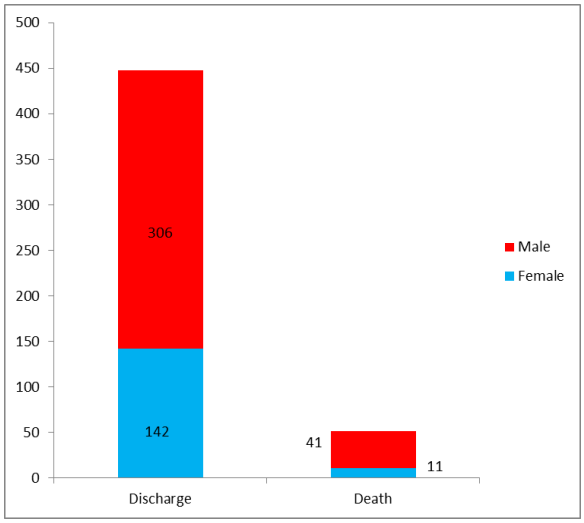
*significant; ns= not significant ; ** highly significant

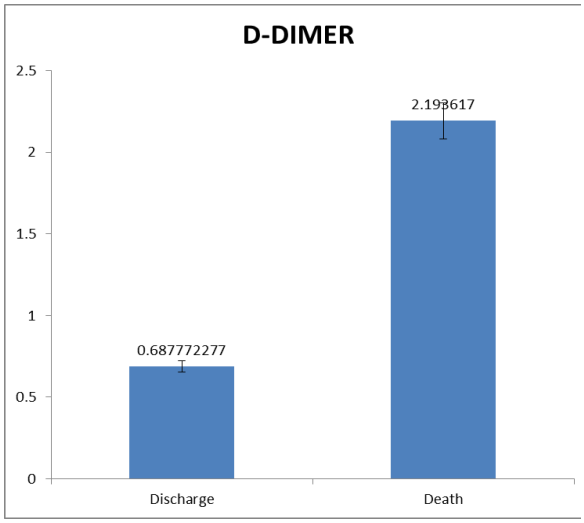
Correlation analysis of laboratory biomarkers with C.T. score

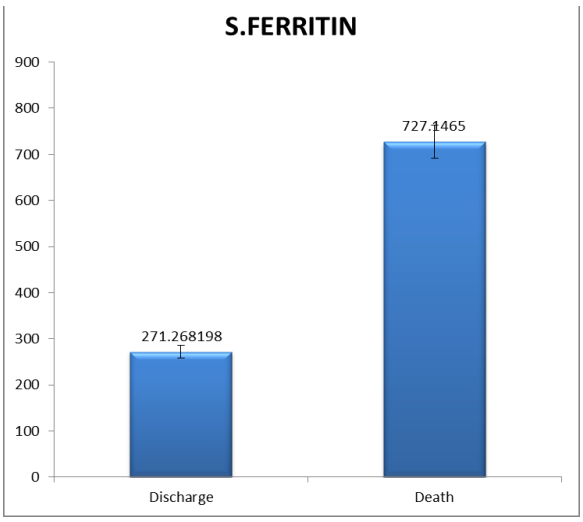
Results showed that the D-dimer ($R = -0.25$; $P < 0.01$) was negatively correlated with C.T. score, with a significant difference ($p<0.05$). Whereas ferritin ($R = 0.11$; $P = 0.15$) was negatively correlated with C.T. score, without significant difference ($p>0.05$). This suggests that a significant increase in C.T. score along with D-dimer was the signal of lung deterioration and progression.

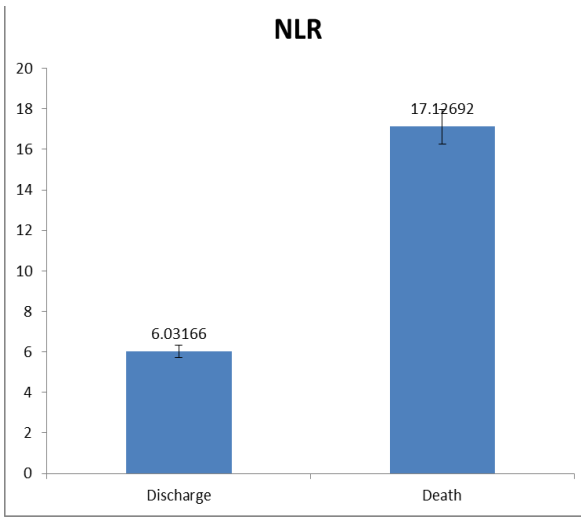
Table 2: D-dimer diagnosis and S-ferritin diagnosis in the prediction of COVID- 19 outcome

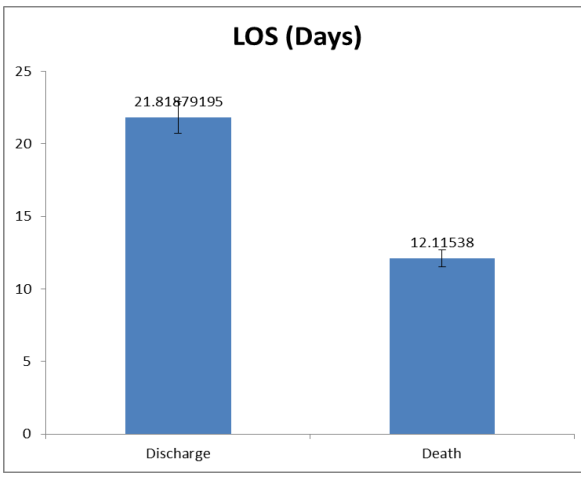
	S-ferritin	D- dimer
Area under curve (AUC):	0.598[95% CI: 0.473, 0.712]	0.880 [95%CI: 0.531, 0.995]
Optimal cut-off	727 ng/ mL	2.2 µg/dL
positive predictive value	35.5%	72.5%
negative predictive value	76.5%	88%


500
450
400
350
300
250
200
150
100
50
0
306
142
41
11
Male
Female
Discharge
Death


D-DIMER
2.5
2
1.5
1
0.5
0
0.687772277
2.193617
Discharge
Death


S.FERRITIN
900
800
700
600
500
400
300
200
100
0
271.268198
727.1465
Discharge
Death


NLR
20
18
16
14
12
10
8
6
4
2
0
6.03166
17.12692
Discharge
Death


LOS (Days)
25
20
15
10
5
0
21.81879195
12.11538
Discharge
Death

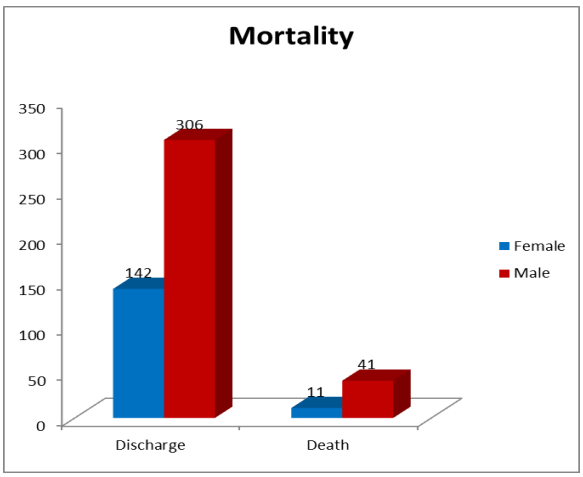

Mortality
350
300
250
200
150
100
50
0
306
142
41
11
Female
Male
Discharge
Death

Figure 1. Laboratory parameters, length of stay, and mortality measurements in COVID-19 patients.

3. DISCUSSION:

Given that most COVID19 fatalities experienced greater lymphopenia, it is reasonable to assume that the lymphocyte count is a rapid and commonly available laboratory parameter that can predict disease severity in COVID19. Leukocytes and neutrophils were also significantly higher in a severe group in a study conducted on 94 patients at Shenzhen Third People's Hospital [7]. Whereas our study results show without significant difference between the expired and survival group NLR ratio. The lymphocyte counts lower than 0.8 × 109/L was associated with COVID-19 severity. The number of neutrophils higher than 3.5 × 109/L may be a poor clinical outcome. Yang et al. reported that the elevated neutrophil-to-lymphocyte ratio (NLR) might predict COVID-19 prognosis [9]. Our study shows that the incidence of mortality in COVID-19 patients aged more than 40 years was 10.4% for patients having NLR >17.

Ferritin is a useful marker to predict the outcomes in COVID-19. Various reports showed that higher ferritin levels, along with CRP and IL-6, were correlated with the worse outcome [10-16]. A positive predictive value of 35.5% and a negative predictive value of 76.5% for the predictor of mortality. The AUC for ferritin is 0.598, with the optimal cutoff 727 ng/mL in predicting the mortality. This suggests that inflammation plays a larger role leading to mortality in younger vs. older adults. In a study by Zhou et al., serum ferritin levels were elevated in non-survivors compared to survivors. It has been reported that hyperferritinemia can activate macrophages, which increases the secretion of pro-inflammatory cytokines, and the subsequent inflammation is mainly responsible for organ damage. Although ferritin is known as a positive acute phase reactant and serum level of ferritin intracellular protein increases during inflammation, dying cells may also release the ferritin.

D-dimer will originate from the formation and lysis of crosslinked fibrin and, it reflects the activation of both the coagulation and fibrinolysis. Covid-19 was associated with hemostatic abnormalities and elevated D-dimer levels, especially in death cases. The AUC for D- dimer at admission was 0.880, with an optimal cutoff of 2.2 µg/dL in predicting the cause of mortality. Hence, the AUC of serum ferritin 0.598 represents the poor ability to discriminate the prediction for the cause of death than D-dimer levels. Similarly, Ning et al. also reported the abnormal coagulation results in elevated D-dimer in deaths with Covid-19.

Elevation of D-dimer indicates the hypercoagulable state, which may be attributed to different reasons, like the virus infection usually comes with a proinflammatory response and insufficient control of an anti-inflammatory response. This might be due to the dysfunction of endothelial cells, resulting in excess thrombin generation. Second, the hypoxia observed in severe Covid-19 can stimulate thrombosis by increasing blood viscosity and a hypoxia-inducible transcription factor. Third, severe patients in the hospital were more prone to have older ages, underlying conditions, long-term bed rest, and risk factors in thrombosis [17-25].

Our study found that D-dimer increased significantly at the initial stage in severe COVID-19 patients, while no significant difference in the C.T. scores was found between the severe and mild groups. Furthermore, ROC further confirmed that D-dimer was an early biomarker for predicting the severity of COVID-19 with good performance. Our study found that lymphocytes progressively decreased and rebound in the recovery stage. Hence, NLR shows a similar trend; it progressively increased and decreased at the recovery stage.

A D- dimer positive predictive value of 72.5% and a negative predictive value of 88% for the predictor of mortality. A ferritin positive predictive value of 35.5% and a negative predictive value of 76.5% for the predictor of mortality. Hence, the AUC of serum ferritin 0.598

represents the poor ability to discriminate the prediction for the cause of death than D-dimer levels. D-dimer > 2 μg/dL on admission was associated with in-hospital death.
These main findings indicate that D-dimer on admission >2.0 μg/dl was the independent predictor of hospital death in patients with Covid-19.
CONCLUSION:
D-dimer <2.0 μg/dl at admission is the optimum cutoff to predict in-hospital mortality for Covid-19. In-hospital mortality is significantly high in patients with D-dimer ≥ 2.0 μg/dl than those with D-dimer < 2.0 μg/dl on admission. Among other laboratory tests, D-dimer gives the best early marker of diagnosis to improve the management of Covid-19 patients.
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