Original Article

The second wave of COVID-19 wreaked havoc: A look at clinical and laboratory parameters of survivors and non-survivors admitted to Intensive Care Unit, a single-centered retrospective study

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Abstract

Background: The second wave of COVID-19 was disastrous and claimed many lives in India and abroad. The most challenging task was to provide the required treatment as per the patient's condition, within a limited span of time. The lack of prognostic predictors at the time of admission led to failure in prioritizing the patient's need for intensive care. **Aim:** This study was conducted to find out the clinical and laboratory parameters at the time of admission to ICU as predictors of outcomes in COVID-19 patients, which can help in judicious utilization of the available resources for better patient care. **Subjects and Methods:** Study comprises of 161 ICU admitted patients. Study of clinical traits, comorbidities, test results, and demographic variables were carried out among survivors and non-survivor. **Result:** Maximum death were patients of age group 21–30 years and male gender. Mortality in hypertensives, diabetics, and patients with sepsis were found to be statistically significant. Patients who developed ARDS and pneumonia or needed ventilation died invariably. High levels of laboratory parameters like IL-6, LDH, PT, INR, aPTT, ferritin, WBC count, and D-dimer were significantly associated with poor outcomes and at a particular cutoff had optimum sensitivity and specificity to predict mortality in ICU admitted COVID-19 patients. At the same time, low lymphocyte count and PaO2/FiO2 ratio was significantly associated with bad prognosis ($P < 0.05$). **Conclusion:** This paper will help in prioritizing patients in ICU who need special attention especially at the time of meager supply of resources.

Keywords: COVID-19, D-dimer, diabetes, hypertension, ICU, LDH, mechanical ventilation

Introduction

The devastating second wave of COVID-19 wreaked havoc in India. Officials and health experts had flagged an increasing trend of cases being reported from the rural districts of Bihar which was 9–10 times more than the first wave peak. Patna stood on the crest of the hill with five more nearby districts as runner-up.[1,2] All India Institute of Medical Sciences (AIIMS) Patna was stuffed with severe cases of COVID-19 during the months of February to June with a peak in March and April 2021.

Till date, meticulous/finest supportive care was the only foundation for ensuring people who are critically ill and

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Table 1: Baseline characteristics of study subjects Mean age: 53.8±16.0 years

Characteristic	No.	Percentage
Age		
21-30	15	9.4
31-40	21	13.0
41-50	33	20.5
51-60	35	21.7
>60	57	35.4
Gender		
Male	111	68.9
Female	50	31.1
Hypertension		
Yes	68	42.2
No	93	57.8
Diabetes		
Yes	50	31.1
No	111	68.9
Pneumonia		
Yes	21	13.0
No	140	87.0
ARDS		
Yes	10	6.2
No	151	93.8
CVD		
Yes	7	4.3
No	154	95.7
Sepsis		
Yes	8	5.0
No	153	95.0
Respiratory Rate		
Normal	109	67.7
Raised	52	32.3

Table 2: Shows the number of survivors and non-survivors

	Frequency	Percent
Non-survivors	67	41.6
Survivors	94	58.4
Total	161	100.0

admitted to the Intensive Care Unit (ICU) have the best chances of survival. But the discrete and disparate outcomes of severe COVID-19 patients requiring ICU admission, from good prognosis to that in need of mechanical ventilation (MV) and proceeding further to mortality have been challenging for physicians from the very beginning of this pandemic, as to identify at-risk patients and provide them intensive attention.[3] Data from epidemiological studies have shown that 6 to 12% of patients turn out to be severe and require admission to ICU due to acute hypoxemic respiratory failure and many among them require intensive MV. The reported mortality rate among patients admitted to ICU ranges from 50–65% and this range hikes further to 97% in patients requiring MV.[4] Besides MV, there may be other linked clinical parameters, laboratory findings, and associated comorbidities that may be responsible for adverse outcomes and death in critically ill SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) patients.

Pathological data relating to this cohort of fatal cases during the second wave are sparse.[5] Analysis of morbidity and mortality among a cohort of ICU admitted patients of COVID-19 will give a better understanding of the pathogenesis of this disease. Also, clinical parameters, laboratory findings, and associated comorbidities were found to be significantly different between survivors and non-survivors and may be incorporated into the future clinical prognosis model. Special care and meticulous attention may be paid to those from the very beginning who have these parameters deranged beyond their cutoffs at the time of admission to ICU.

Material and Method

This was a retrospective observational cohort study. All ICU admitted patients of severe COVID-19 at our center during the second wave of COVID-19 from March 2021 to June 2021 were incorporated in the study. A total of 161 patients were enrolled. The study was approved by the Institutional Ethics committee of AIIMS Patna and being a retrospective study, no informed consent was required. After taking written permission from the institute, data of ICU admitted patients from the month of March to June 2021 were retrieved from the Medical record department. It included demographic details of the patients, e.g., age and sex, associated comorbidities, e.g., asthma, COPD, diabetes, hypertension, renal disease, liver disease, immunosuppressive disease, cancer, or any immunosuppressive medications, and clinical details of patients. Laboratory parameters at the time of admission to ICU were retrieved from the hospital information system. Also, the final outcome of patients, i.e., discharged or deceased, was taken into account. Accordingly, the patients were divided into two groups:

Group I: Survivors (Those patients who were discharged from ICU after treatment)

Group II: Non-Survivors (Those patients who died in the ICU during treatment, i.e., deceased)

SPSS version 23.0 was used for data analysis.

Result

In our 161 study subjects, mean age was found to be 53.8 years plus minus 16 years, with maximum number of subjects belonging to >60 years age group 35.4% (57/161). The majority of subjects were males 68.9% (111/161). Other baseline comorbidities in the subjects at the time of admission were, hypertension in 42.2% (68/161), diabetes in 31.1% (50/161), pneumonia in 13% (21/161), Acute Respiratory Distress Syndrome (ARDS) in 6.2% (10/161), Cardio Vascular Disease (CVD) in 4.3% (7/161), sepsis in 5% (8/161), and increased respiratory rate in 32.3% (52/161) [Table 1].

Out of the 161 subjects included in our study 58.4% (94/161) were survivors while the remaining 41.6% (67/161) died during their stay in our hospital [Table 2].

Mortality from COVID-19 disease among study subjects was maximum for those belonging to the 21–30-year age group 46.7% (7/15), while it was least among those between 41 and 50 years 33.3% (11/33). The association between COVID-19 mortality and the age of the study subjects was not found to be statistically significant.

Mortality from COVID-19 disease was revealed to be more than twice among males as compared to their female counterparts and the association of disease mortality with gender was statistically significant.

Mortality among the hypertensives was 54.4% (37/68), as compared to 32.3% (30/93) among non-hypertensives, and the association between disease mortality and hypertension was found to be statistically significant.

Diabetes was found to contribute significantly to mortalities in COVID-19 patients with mortalities in diabetics accounting for 56% (28/50), in comparison with 35.1% (39/111) in non-diabetics, and the association between disease mortality and diabetes was found to be statistically significant.

Mortality among COVID-19 patients with sepsis was found to be 100% (8/8), and 38.6% (59/153) of COVID-19 patients without sepsis also succumbed to death. The association between disease mortality and sepsis was found to be statistically significant.

Mortality among the COVID-19 patients with CVD (cardiovascular disease) was found to be 28.6% (2/7) in comparison with 42.2% (65/154) mortality in patients not having CVD. The association between disease mortality and CVD was not found to be statistically significant.

The association between respiratory rate and death among COVID-19 patients was not found to be statistically significant, as mortalities among patients with a high respiratory rate were 42.3% (22/52) in comparison with 41.3% (45/109) in patients with a normal respiratory rate.

Mortalities among COVID-19 patients with ARDS (adult respiratory distress syndrome) and pneumonia were found to be 100% (10/10 & 21/21, respectively) in comparison with 37.7% (57/151) and 32.9% (46/140) mortalities in patients not having ARDS and pneumonia, respectively. These associations between disease mortality with ARDS and pneumonia were found to be statistically significant.

One hundred percent (7/7) of COVID-19 patients who needed a ventilator for maintenance of PaO2 succumbed to death later on in comparison with 39% (60/154) of patients who did not require ventilatory support and died. This association between disease mortality and the need for ventilatory support was found to be highly significant [Table 3].

Mean interleukin-6 (IL-6), lactate dehydrogenase (LDH), prothrombin time (PT), activated partial thromboplastin clotting time (aPTT), ferritin, white blood cell (WBC) count, D-dimer were significantly higher among non-survivors than survivors. Lymphocyte count and PaO2/FiO2 were significantly lower among non-survivors than survivors [Table 4].

The area under the curve (AUC) for different study variables ranged from 72% to 84%, maximum for LDH. Cutoff levels for sensitivity for different study variables are shown in [Table 5].

The cutoff value of IL-6 at the time of admission to ICU was 20.6 pg/ml for ICU survivors relative to non-survivors, and at this cutoff value, the optimum sensitivity and specificity were found to be 88% and 61%, respectively. The mean AUC was 0.78 with a 95% CI of 0.71–0.85 [Figure 1].

The cutoff value of LDH was 575.5 U/L for ICU survivors relative to non-survivors, and at this cutoff value, the optimum sensitivity and specificity were found to be 98% and 84%, respectively. The mean AUC was 0.84 with a 95% CI of 0.78–0.91 [Figure 2].

The cutoff value of PT was 11.7 seconds for ICU survivors relative to non-survivors, and at this cutoff value, the optimum sensitivity and specificity were found to be 89% and 77%, respectively. The mean AUC was 0.72 with a 95% CI of 0.64–0.80 [Figure 3].

The cutoff value of INR was 0.87 for ICU survivors relative to non-survivors, and at this cutoff value, the optimum sensitivity and specificity were found to be 86% and 70%, respectively. The mean AUC was 0.72 with a 95% CI of 0.64–0.80 [Figure 4].

The cutoff value of aPTT was 24.4 seconds for ICU survivors relative to non-survivors, and at this cutoff value, the optimum sensitivity and specificity were found to be 86% and 70%, respectively. The mean AUC was 0.76 with a 95% CI of 0.64–0.80 [Figure 5].

The cutoff value of ferritin was 561 ng/ml for ICU survivors relative to non-survivors, and at this cutoff value, the optimum

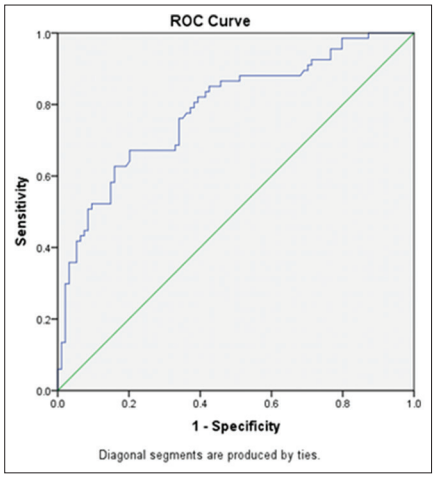

Figure 1: ROC curve for prediction of cutoff value for IL-6

Table 3: Association of COVID-19 mortality with baseline characteristics

Variable	Survivors *n* (%)	Non-survivors *n* (%)	Total	Test of significance
Age				
21-30	8 (53.3)	7 (46.7)	15 (100.0)	χ^2=1.59
31-40	13 (61.9)	8 (38.1)	21 (100.0)	Df=4
41-50	22 (66.7)	11 (33.3)	33 (100.0)	*P*=0.8
51-60	20 (57.1)	15 (42.9)	35 (100.0)	
>60	31 (54.4)	26 (45.6)	57 (100.0)	
Gender				χ^2=9.62
Male	56 (50.5)	55 (49.5)	111 (100.0)	Df=1
Female	38 (76.0)	12 (24.0)	50 (100.0)	*P*=0.002
Hypertension				χ^2=7.93
Yes	31 (45.6)	37 (54.4)	68 (100.0)	Df=1
No	63 (67.7)	30 (32.3)	93 (100.0)	*P*=0.005
Diabetes				χ^2=6.17
Yes	22 (44.0)	28 (56.0)	50 (100.0)	Df=1
No	72 (64.9)	39 (35.1)	111 (100.0)	*P*=0.01
Sepsis				Fisher's exact test
Yes	0 (0.0)	8 (100.0)	8 (100.0)	Df=1
No	94 (61.4)	59 (38.6)	153 (100.0)	*P*=0.001
CVD				Fisher's exact test
Yes	5 (71.4)	2 (28.6)	7 (100.0)	Df=1
No	89 (57.8)	65 (42.2)	154 (100.0)	*P*=0.7
Respiratory Rate				χ^2=0.02
Normal	64 (58.7)	45 (41.3)	109 (100.0)	Df=1
Raised	30 (57.7)	22 (42.3)	52 (100.0)	*P*=0.90
ARDS				Fisher's exact test
Yes	0 (0.0)	10 (100.0)	10 (100.0)	Df=1
No	94 (62.3)	57 (37.7)	151 (100.0)	*P*=0.000
Pneumonia				Fisher's exact test
Yes	0 (0.0)	21 (100.0)	21 (100.0)	Df=1
No	94 (67.1)	46 (32.9)	140 (100.0)	*P*=0.000
Ventilator				Fisher's exact test
Yes	0 (0.0)	7 (100.0)	7 (100.0)	Df=1
No	94 (61.0)	60 (39.0)	154 (100.0)	*P*=0.002

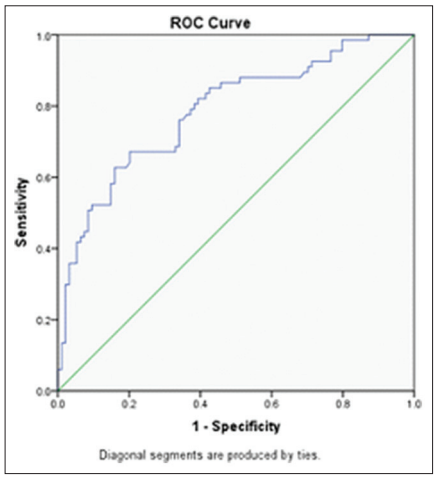

Figure 2: ROC curve for prediction of cutoff value for LDH

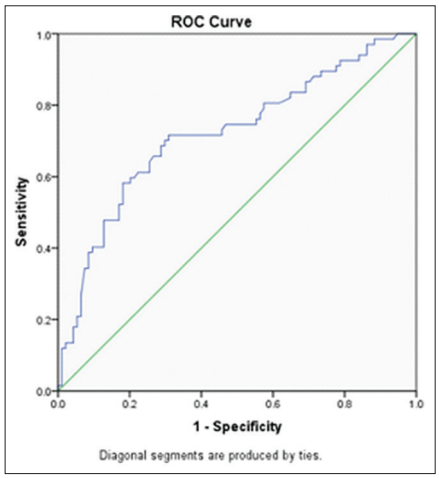

Figure 3: ROC curve for prediction of cutoff value for PT

sensitivity and specificity were found to be 89% and 55%, respectively. The mean AUC was 0.74 with a 95% CI of 0.66–0.81 [Figure 6].

The cutoff value of WBC was 6.42 × 10^9/L ICU survivors relative to non-survivors, and at this cutoff value, the optimum sensitivity and specificity were found to be 89% and 70%, respectively. The mean AUC was 0.73 with a 95% CI of 0.65–0.80 [Figure 7].

The cutoff value of D-dimer was 1.02 μg/ml for ICU survivors relative to non-survivors, and at this cutoff value, the

Table 4: Association of COVID-19 mortality with biochemical parameters

Variable	Survivors (mean±SD)	Non-survivors (mean±SD)	Confidence interval	Test of significance
IL-6 (pg/ml)	35.3±69.8	225.8±684.6	−330.8 to−50.2	T=−2.68 Df=159 *P*=0.008
LDH (U/L)	893.7±387.2	1658.8±775.2	−948.4 to−581.7	T=−8.24 Df=159 *P*=0.000
Total bilirubin (mg/dl)	1.35±6.22	0.97±1.01	−1.13 to 1.89	T=0.62 Df=159 *P*=0.62
Direct bilirubin (mg/dl)	0.23±0.15	0.37±0.57	−0.262 to−0.02	T=−2.27 Df=159 *P*=0.02
PT (seconds)	12.9±2.5	15. ± 7.3	−3.8 to−0.6	T=2.81 Df=159 *P*=0.005
INR	0.95±0.20	1.06±0.17	−0.17 to−0.05	T=−3.63 Df=159 *P*=0.000
aPTT (seconds)	26.3±4.9	34.2±19.5	−12.1 to−3.8	T=−3.78 Df=159 *P*=0.000
Ferritin (ng/ml)	679.9±485.7	1073.1±624.3	−566.0 to−220.2	T=−4.49 Df=159 *P*=0.000
WBC ($\times10^9$/L)	9.8±5.7	15.2±8.0	−7.4 to−3.2	T=−4.92 Df=159 *P*=0.000
Lymphocyte ($\times10^9$/L)	14.9±10.7	8.2±6.5	3.8 to 9.6	T=4.58 Df=159 *P*=0.000
D-Dimer (µg/ml)	1.56±1.53	4.62±5.10	−4.16 to−1.95	T=−5.48 Df=159 *P*=0.000
PaO2/FiO2	458.8±66.9	234.9±152.4	188.9 to 258.8	T=12.64 Df=159 *P*=0.000

Table 5: ROC Curve

Variable	AUC	SE	Confidence interval	Significance	Cutoff value	Sensitivity	1-Specificity
IL6 (pg/ml)	0.78	0.04	0.71-0.85	<0.001	20.6	0.88	0.61
LDH (U/L)	0.84	0.03	0.78-0.91	<0.001	575.5	0.98	0.84
PT (seconds)	0.72	0.04	0.64-0.80	<0.001	11.7	0.89	0.77
INR	0.72	0.04	0.64-0.80	<0.001	0.87	0.86	0.70
aPTT (seconds)	0.76	0.04	0.68-0.84	<0.001	24.4	0.86	0.70
Ferritin (ng/ml)	0.74	0.04	0.66-0.81	<0.001	561	0.89	0.55
WBC ($\times10^9$/L)	0.73	0.04	0.65-0.80	<0.001	6.42	0.89	0.70
D-Dimer (µg/ml)	0.76	0.04	0.68-0.83	<0.001	1.2	0.83	0.63

optimum sensitivity and specificity were found to be 83% and 63%, respectively. The mean AUC was 0.76 with a 95% CI of 0.68–0.83 [Figure 8].

Discussion

The second wave of COVID-19 had caused visible strain on the healthcare system, leaving hospitals struggling to cope with the short supply of life-saving measures like oxygen and critical drugs.[6] So, identifying risk factors for early progression toward severe disease and or mortality is fundamental for the practical management of COVID-19 patients.

In this cohort of ICU admitted patients, the male gender predominates among the deceased. A possible explanation is a higher expression of angiotensin-converting enzyme-2 (ACE-2) receptor in males which is the receptor for coronavirus. Immunological differences based on sex hormones and X

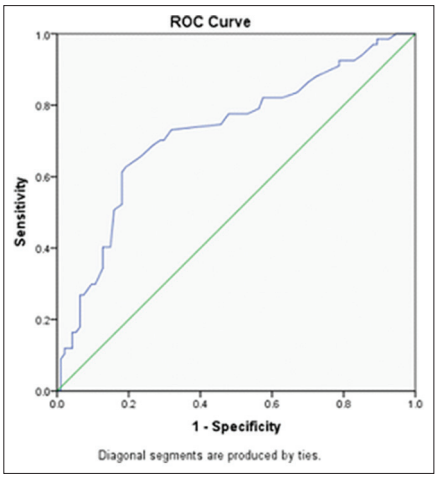

Figure 4: ROC curve for prediction of cutoff value for INR

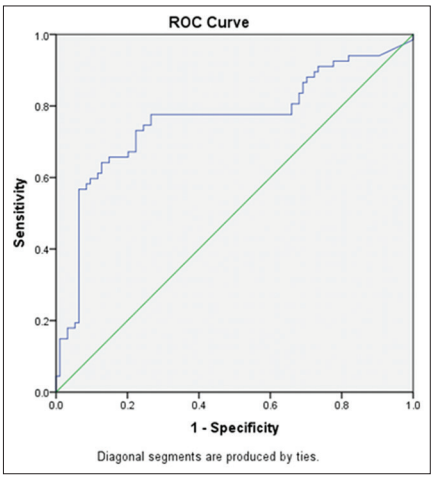

Figure 5: ROC curve for prediction of cutoff value for aPTT, not APTT

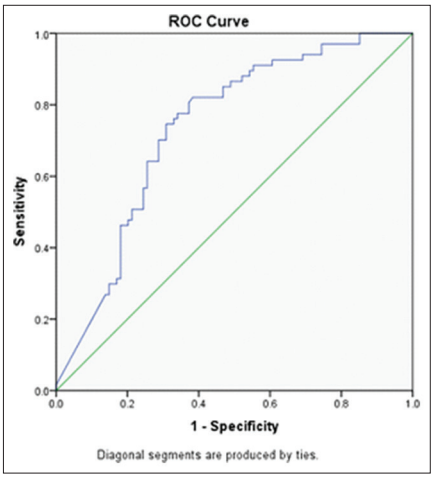

Figure 6: ROC curve for prediction of cutoff value for Ferritin

chromosome, smoking and drinking among men more than females, and more sincerity to follow COVID-19 guidelines among females may be the other possible explanation for the increased incidence of COVID-19 among males.[7]

According to ICMR, young generations were increasingly involved in the second wave because they were the ones who went out for work and there were mutant variants also prevalent in the nation which were affecting them. However, people above the age of forty were more vulnerable to the adverse outcome as seen in our study.[8]

In a study done by Grifoni *et al.*,[9] the mean level of IL-6 in patients who met the criteria for composite endpoint was significantly higher for those patients who did not (134.3 ± 19.5 vs 15.6 ± 14.8 pg/ml, respectively. $P < 0.0001$). In our study, the mean IL-6 level among deceased and discharged was 225.8 ± 684.6 vs 35.3 ± 69.8, respectively, $P = 0.008$). At a cutoff of 20.6 pg/ml and having sensitivity and specificity of 88% and 61%, respectively, clearly discriminate between ICU admitted deceased and discharged, similar to the study done by Guirao *et al.*[10] where a cutoff point of 35 pg/ml could clearly differentiate patients with more severe disease.

A study done by Henry *et al.*[11] has demonstrated a significant association between elevated LDH values and worse outcomes in patients with COVID-19. The cause of abnormal value may be multiple organ injury and decreased oxygenation with upregulation of glycolytic activity. Isoenzyme 3 of LDH is present in lung tissue. So, patients with a severe grade of COVID-19 release a greater amount of LDH in circulation, as a severe form of interstitial pneumonia.

In a study done by Araya *et al.*,[12] coagulopathy and abnormal coagulation parameters were indicated among the most significant biomarkers of poor prognosis. Our study has shown a significantly raised level of PT, INR, & APTT at the time of admission to ICU who died later on than those who survived. The prolonged PT and APTT in those who died might indicate activation of the coagulation mechanism and consumption of coagulation factors.[13]

In a study done by Ahmed *et al.*,[14] the optimal cutoff of ferritin for predicting mortality was 574.5 ng/ml with sensitivity and specificity of 82% and 51%, respectively, similar to our study where a cutoff of 561 ng/ml with sensitivity and specificity of 89% and 55% could clearly differentiate between deceased and discharged.

WBC was significantly raised among the patients admitted to ICU who died later on as compared to those who survived. Elevated WBC level indicates bacterial infection and lymphocytopenia indicates a viral infection. The possible explanation is that coronavirus may have infected blood cells via CD13 or CD66A and may also induce autoantibodies and immune complexes to damage these cells. Also, there was glucocorticoid treatment going on, which may be the reason for lymphocytopenia in these patients.[15] In a study done by Zhu *et al.*,[16] there was a significant association between WBC count and death, and a cutoff value of $>6.16 \times 10^9$/L predicts death almost similar to our study in which a WBC count of 6.42×10^9/L at the time of admission

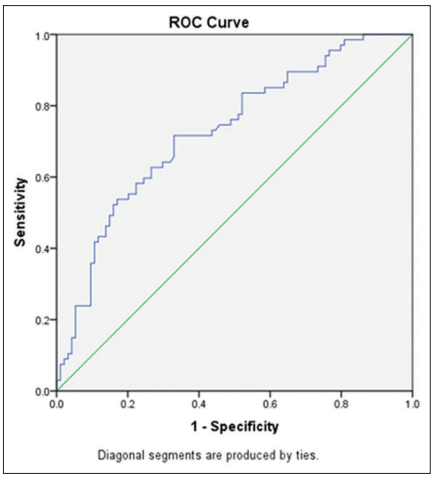

Figure 7: ROC curve for prediction of cutoff value for WBC count

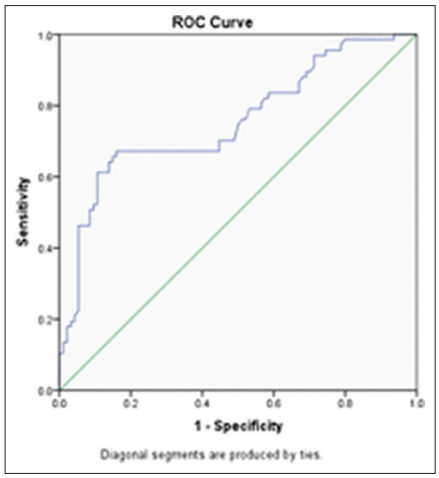

Figure 8: ROC curve for prediction of cutoff value for D-dimer

to ICU predicts mortality in COVID patient with sensitivity and specificity of 89% and 70%, respectively, and AUC of 0.73.

In a study done by Poudel *et al.*,[17] the D-dimer value at an optimal cutoff of 1.5 μg/ml predicts mortality in COVID-19 patients, almost similar to our study at a cutoff of 1.2 μg/ml with AUC of 0.76 and sensitivity and specificity 80% and 56%, respectively, could predict mortality among ICU admitted COVID-19 patients.

There was a significant difference in the PiO2/FiO2 (P/F) ratio at the time of admission to ICU among patients who were deceased or discharged later on (234.9 ± 152.4 and 458.8 ± 66.9, respectively, *P* value 0.000). According to the Berlins definition, ARDS is a P/F ratio <300 mmHg and its severity correlates with mortality.[18,19]

Most of the patients who died had underlying diseases prior to infection with COVID-19 which likely contributed to the risk of death. Significant findings among the deceased were the presence of diabetes, hypertension, and sepsis. There was also a significant association between the presence of ARDS, pneumonia, and the need for ventilator at the time of ICU admission to the mortality of patients. In a study done by Pawar *et al.*,[20] people with comorbidities had significant association to death. Immunization history should have been taken into consideration in order to assess risk of comorbidities with respect to varying immunization status of patient.[21]

So this study shows that IL-6, LDH, PT, aPTT, INR, ferritin, D-dimer, at a particular cutoff at the time of admission to ICU along with the presence of some chronic disease, and need for a ventilator at the time of admission to ICU can offer a tangible solution for prioritizing patient who needs utmost care from the very beginning of admission to ICU to give the best result and efficient patient recovery without undue strain on the health system.

This paper will groom the knowledge of primary care physicians regarding the clinical parameters, associated comorbidities, and laboratory findings with their cutoffs beyond which they decide mortality in serious patients of COVID-19.

Conclusion

This study will help in triaging patients who need special care and meticulous attention from very beginning of their admission to ICU especially in situations of undue strain on healthcare system with respect to under supply of life-saving measures and drugs as happened during second wave of COVID-19. The second wave was more devastating and ravaging than the first, we do not know how many such waves, or how soon, will be faced in the future, but we will definitely know how to fight better next time.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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