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A study of COVID-19 laboratory findings and chest CT findings in assessing disease severity in patients in western Maharashtra

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***Abstract*---**Background: Coronavirus disease-19 (COVID-19) has become a world health threat. Early detection of high-risk patients with laboratory and radiological parameters can aid in reducing mortality. Aims and objectives: To assess the clinical, laboratory, radiological parameters in patients with COVID-19 and to compare them with the outcome. Material and methods: The study was conducted in 200 patients presenting with COVID-19 infection in a tertiary care hospital over one month during month of October 2021. Enrolled patients underwent inflammatory markers, haematological markers and CT scan of the thorax on admission. Statistical analysis: Appropriate statistical tests were applied using SPSS software v21 for analysis; p-value<0.05 was considered statistically significant. Mean age of the study population was 51.84(SD±16.02). D-dimer, CRP, ferritin, TLC, NLR, CTSS has shown significant correlation with mortality. Mean CTSS was 9.75 (SD±5.32), mean D-dimer was 0.79 (SD±1.69), mean sr. ferritin was 320.68 (SD±328.04), the mean CRP level was 2.08 (SD±5.86) and mean neutrophil-lymphocyte ratio (NLR) was 5.01 (SD±5.53). The PaO2/FiO2 ratio was identified as an independent risk factor (odd ratio [OR] = 0.992, 95% confidence interval [CI]: 0.986–0.998, p = 0.006). The area under curve of the receiver operator characteristic (AUROC) of PaO2/FiO2 with mortality as outcome was 0.795 (95% CI: 0.684–0.906, p < 0.0001). Conclusion: PaO2/FiO2 ratio can potentially be used as an independent risk factors for predicting mortality in COVID-19 patients requiring intensive care. Thus, clinicians can consider the inflammatory markers and PaO2/FiO2 ratio in particular and take active steps required to reduce the mortality from COVID-19.

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***Keywords*---**COVID-19, inflammatory markers, CRP, total leucocyte count, neutrophil lymphocyte ratio, ferritin.

Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been implicated as the virus which is responsible for SARS-CoV-2 disease (COVID-19), which spread worldwide since December 2019. [1] The clinical spectrum of the disease varies from asymptomatic infection, mild upper respiratory symptoms to severe pneumonia with respiratory failure and even death. The most common symptoms at onset of SARS-CoV 2 illness are fever, cough, ache, dyspnoea, haemoptysis and diarrhoea. The severe symptoms of SARS-CoV 2 are associated with an increase rate of fatalities. [2] The severity of COVID-19 resides in the development of large quantities of proinflammatory cytokines that can eventually contribute to acute respiratory distress syndrome (ARDS) and multiple organ failure (MOF).[3] There is ever-growing evidence that in critically ill and those with severe disease, there are characteristics of hyperinflammation, which comprise of elevated serum C-reactive protein levels (CRP), procalcitonin levels (PCT), D-dimer, and ferritin. These findings suggest a potential critical role of cytokine storm in the pathophysiology of COVID-19.[4] Each of the laboratory parameters do have a potential value for risk stratification and the prediction of COVID-19 outcomes.[5] Inflammatory markers such as serum ferritin, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and interleukin-6 (IL-6) have been reported to be of significant association with the increased risk of the development of severe COVID-19.[6,7] If those patients with high risk of mortality are be identified early on admission to the ICU, it would be useful in providing more efforts in focused treatment on these patients to reduce the mortality from COVID-19. This study is designed to investigate the various laboratory markers and chest CT severity score and their correlation with the severity of disease.

Material and Methods

Aims and objectives: To assess the clinical, laboratory, radiological parameters in patients with COVID-19 and to compare them with the outcome. Study design: This was a single centre, retrospective, comparative study done on patients with COVID-19 infection. This study was conducted in KIMS Hospital, Medicine department over period of 1 month. Study sample: The study was conducted in 200 patients presenting with COVID-19 infection in a tertiary care hospital. Study setting: This study was conducted in KIMS Hospital, over period of one month during month of October 2021. The Institutional Ethical committee approval was taken (protocol number: 376/2020-2021). Inclusion criteria were patients with COVID-19 pneumonia with at least one positive RT-PCR test for COVID-19 with a known endpoint of the disease. The patient with hepatic and renal dysfunction and those with history of ischemic heart disease and ischemic stroke were excluded from this study. All enrolled patients underwent inflammation markers (CRP, D-Dimer, Sr. Ferritin, IL-6), haematological markers (Haemoglobin, Neutrophil, Lymphocyte, Leucocyte count) and high-resolution CT scan of the thorax on admission. Cut-offs for D-dimer, serum ferritin, CRP level, ESR, procalcitonin, IL-6 and TLC were taken as 0.5mg/L, 274ng/ml in males and 204

ng/ml in females, 0.6mg/dl, 15mm/hr, >0.5ng/ml and >2pg/ml. All enrolled patients received the standard treatment for COVID-19 as per standard reference guidelines. Raw material will be collected from trained medical staff using the medical records. Data will be double checked for correctness, subsequently anonymized and transferred to the first authors for data analysis. We aim to study and compare the laboratory parameters and the radiological parameters of moderate to severe COVID-19 patients. Statistical analysis: Data Collected was analysed for mean, percentage, standard deviation and chi square test for quantitative data by using Microsoft excel spread sheet. Appropriate statistical tests were applied using SPSS software version 21 (trial version) for analysis and 'p' value < 0.05 was considered as statistically significant.

Results

In the present study, the mean age of the study population was 51.84(SD±16.02), mean CTSS was 9.75 (SD±5.32), mean D-dimer was 0.79 (SD±1.69) and mean sr. ferritin was 320.68 (SD±328.04). The mean CRP level was 2.08 (SD±5.86), the mean ESR was 43.32 (SD±25.55), mean procalcitonin was 1.96 (SD±3.33) and mean IL-6 was 220.09 (SD±474.66). The mean Arterial pO2 / Fraction of inspired oxygen (P/F ratio) was 293.87 (SD±118.3), mean total leucocyte count was 8402.01 (SD±4721.42) and the mean neutrophil lymphocyte ratio (NLR) was 5.01 (SD±5.53). [Table 1]

Table 1: The mean and standard deviation of numerical variable in COVID-19 patients

Parameter	Mean	± SD
Age	51.84	16.02
Chest CT severity score (CTSS)	9.75	5.32
D-dimer	0.79	1.69
Serum Ferritin	320.68	328.04
C-reactive protein (CRP)	2.08	5.86
Erythrocyte sedimentation rate (ESR)	43.32	25.55
Procalcitonin	1.96	3.33
Interleukin-6 (IL-6)	220.09	474.66
P/F ratio (Arterial pO2 / Fraction of inspired oxygen)	293.87	118.30
Total leucocyte count	8402.01	4721.42
Neutrophil lymphocyte ratio	5.01	5.53

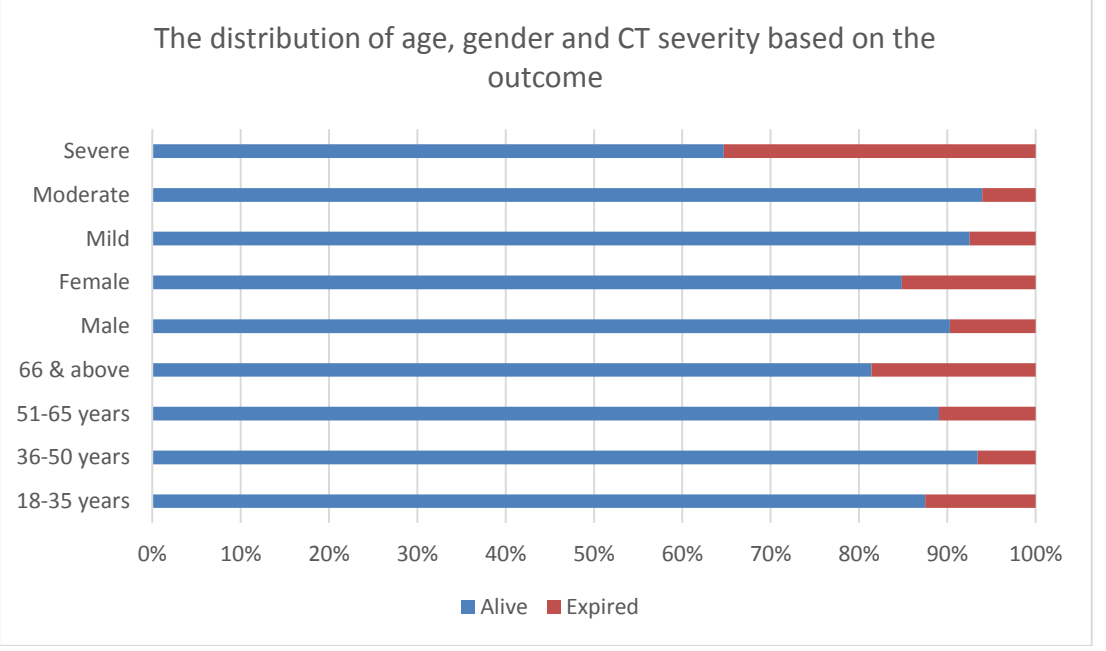
In the present study it was observed that based on the 'Berlin definition', out of 200 patients, 98(32.7%), 62(20.7%), 23(7.7%) and 17(5.7%) of them had no ARDS, mild ARDS, moderate ARDS and severe ARDS respectively. In the present study it was observed that out of 200 patients included in the study, 177 were survived and discharged, whereas 23 of them expired. Considering the age, of those who were survived, 28, 57, 57 and 35 belonged to 18-35 years, 36-50 years, 51-65 years and 66 years & above. Of those who expired, 4, 4, 7 and 8 belonged to 18-35 years, 36-50 years, 51-65 years and 66 years & above. Considering the gender, of those who were survived, 121 were males and 56 were females. Of those who

expired 13 were males and 14 were females. Considering the CT severity, of those who were survived, 62, 93 and 22 of them had mild, moderate and severe severity on CT whereas of those who expired, 5, 6 and 12 of them had mild, moderate and severe severity on CT. [Table 2][Figure 1]

Table 2: The distribution of age, gender and CT severity based on the outcome

		Outcome		Total
		Survivors (177)	Non-Survivors (23)	
Age group	18-35 years	28	4	32
	36-50 years	57	4	61
	51-65 years	57	7	64
	66 & above	35	8	43
Gender	Male	121	13	134
	Female	56	10	66
CT Severity	Mild	62	5	67
	Moderate	93	6	99
	Severe	22	12	34

Figure 1: The distribution of age, gender and CT severity based on the outcome



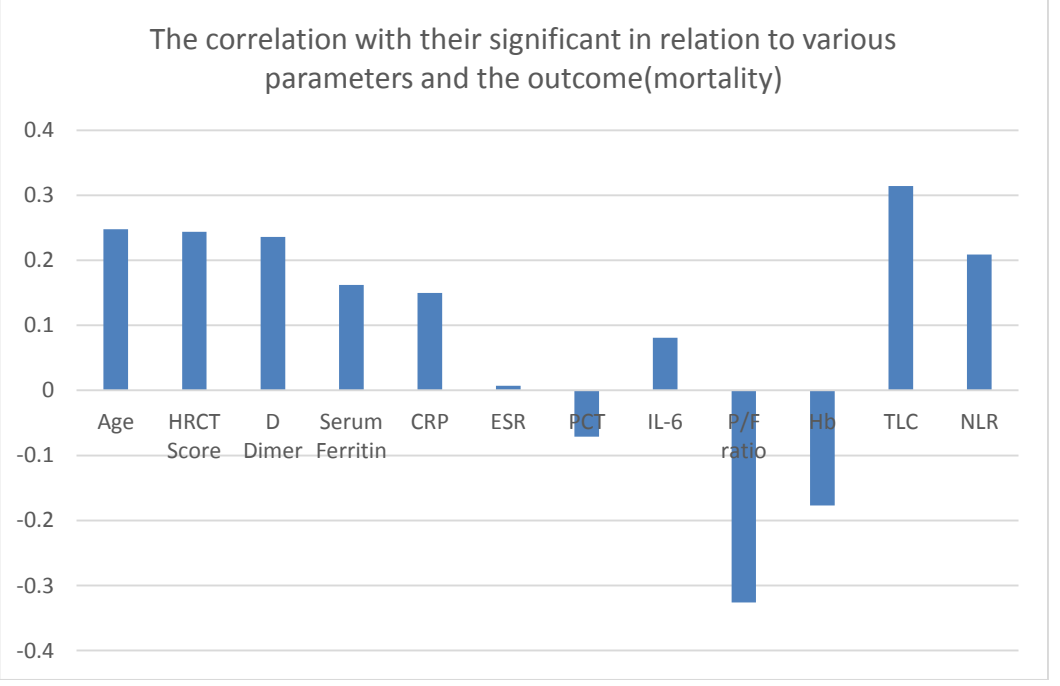
In the present study considering mortality as an outcome, the age (*r=0.249; p<0.001*), HRCT score (*r=0.249; p<0.001*), serum ferritin (*r=0.244; p<0.001*) and C-reactive protein (*r=0.236; p=0.001*) of the patient had a significant positive correlation with mortality. It was observed that Erythrocyte sedimentation rate (*r=0.007; p=0.919*), procalcitonin (*r=-0.71; p=0.321*) and interleukin-6 (*r=0.081; p=0.253*) had positive correlation with mortality which was not significant. It was

observed that P/F ratio (*r=-0.326; p=<0.001*) and haemoglobin (*r=-0.177; p=<0.001*) had a significant negative correlation with mortality as an outcome. It was observed that total leucocyte count (*r=0.314; p=<0.001*) and neutrophil lymphocyte ratio (*r=0.209; p=<0.001*) had a significant positive correlation with mortality as an outcome. [Table 3][Figure 2]

Table 3: The correlation with their significant in relation to various parameters and the outcome(mortality)

Parameter	Correlation (Spearman rho)	P value
Age	0.248	<0.001
Chest CT severity score (CTSS)	0.244	<0.001
D-dimer	0.236	0.001
Serum Ferritin	0.162	0.022
C-reactive protein (CRP)	0.15	0.034
Erythrocyte sedimentation rate (ESR)	0.007	0.919
Procalcitonin	-0.071	0.321
Interleukin-6 (IL-6)	0.081	0.253
P/F ratio	-0.326	<0.001
Haemoglobin	-0.177	<0.001
Total leucocyte count	0.314	<0.001
Neutrophil lymphocyte ratio	0.209	0.003

Figure 2: The correlation with their significant in relation to various parameters and the outcome(mortality)



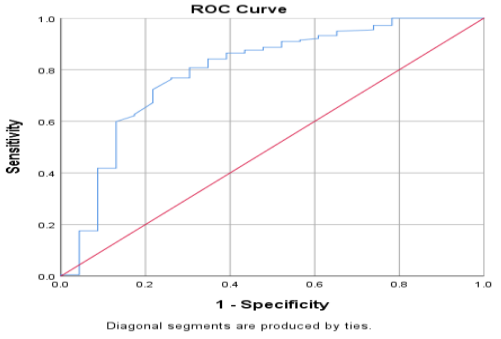
Multivariate analysis using binomial logistic regression was performed to see how factors were independently associated with the outcome after adjusting the other factors. The following were the findings: After adjusting for age, gender, P/F ratio, ferritin, haemoglobin, TLC, D-dimer, CRP level and NLR and severe COVID-19 on CT score, binomial logistic regression analysis was performed to see if they were independently associated with death versus survival. [Table 4]

Table 4: The binomial logistic regression analysis with outcome survival vs mortality with various parameters showing significant association on univariable correlation

Parameter	Sig.	Exp(B)	95% C.I.for EXP(B)	
			Lower	Upper
Severe CT-score	0.203	2.735	0.582	12.85
D-dimer	0.670	1.283	0.408	4.028
Sr. Ferritin	0.815	0.870	0.272	2.785
CRP	0.901	1.081	0.320	3.653
Severe ARDS	0.002	22.586	3.110	164.015
P/F ratio	0.006	0.992	0.986	0.998
Anaemia	0.652	0.745	0.207	2.675
TLC	0.544	1.434	0.448	4.588
NLR	0.192	2.228	0.669	7.426

After adjusting for age, gender, CT severity score, ferritin, haemoglobin, TLC, D-dimer, CRP level and NLR, severe ARDS, (i.e: P/F ratio of ≤100) had around 22 times higher chances of having death as an outcome in comparison to those without ARDS (i.e: P/F ratio of >300) (OR: 22.586; p=0.002; C.I: 3.110-164.015). The PaO2/FiO2 ratio was identified as an independent risk factor (odd ratio [OR] = 0.992, 95% confidence interval [CI]: 0.986–0.998, p = 0.006). The area under curve of the receiver operator characteristic (AUROC) of PaO2/FiO2 with mortality as outcome was 0.795 (95% CI: 0.684–0.906, p < 0.0001) with a sensitivity of 80.8% and a specificity of 69.6% when the cut-off value was 226 mmHg.

Figure 3: Receiver operator characteristic (ROC) curve of PaO2/FiO2 with mortality as outcome



Discussion

It was observed that in the present study, the mean age of the study population was 51.84(SD±16.02) and there was a significant positive correlation of increasing age with mortality as an outcome (*r=0.248;p=<0.001*). The findings are similar to study by *Biswas M et al* patients with age ≥50 years were at a significantly massive risk of mortality compared to those aged <50 years.[8] A study by Ibrahim ME et al reported a significant association between COVID-19 death and increasing age.[9] *Chi et al* noted that elder age (OR 1.06 [95% CI 1.03–1.08], p< 0.001) are independently associated with severe disease at admission.[10] *Chen et al* quoted that cOVID-19 is more likely to infect the older adult men.[11] *Guo YR et al* reported that COVID-19 infection progresses rapidly and leads to death in older patients and those with comorbid conditions.[12] The mean CTSS was 9.75 (SD±5.32), mean D-dimer was 0.79 (SD±1.69) and mean sr. ferritin was 320.68 (SD±328.04). The mean CRP level was 2.08 (SD±5.86), the mean ESR was 43.32 (SD±25.55), mean procalcitonin was 1.96 (SD±3.33) and mean IL-6 was 220.09 (SD±474.66). The mean Arterial pO2 / Fraction of inspired oxygen (P/F ratio) was 293.87 (SD±118.3), mean total leucocyte count was 8402.01 (SD±4721.42) and the mean neutrophil lymphocyte ratio (NLR) was 5.01 (SD±5.53).

In the present study considering mortality as an outcome, the age (*r=0.249; p<0.001*), HRCT score (*r=0.249; p<0.001*), serum ferritin (*r=0.244; p<0.001*) and C-reactive protein (*r=0.236; p=0.001*) of the patient had a significant positive correlation with mortality. It was observed that P/F ratio (*r=-0.326; p=<0.001*) and haemoglobin (*r=-0.177; p=<0.001*) had a significant negative correlation with mortality as an outcome. It was observed that total leucocyte count (*r=0.314; p=<0.001*) and neutrophil lymphocyte ratio (*r=0.209; p=<0.001*) had a significant positive correlation with mortality as an outcome. The findings of the present study were compared to similar studies who compared inflammatory markers, haematological markers and CT severity score with disease severity and mortality. [Table 5]

Table 5: Similar studies who compared inflammatory markers, haematological markers and CT severity score with disease severity and mortality

Author	Sample size	Type of study	Results	Inference
Asghar MS et al (2020)	373	Retrospective, observational	Non-surviving patients had shown a lower, significantly increased TLC, elevated D-dimer levels and elevated PCT.	Inflammatory markers like LDH, PCT, D-dimer, CRP, and ferritin are a useful guide for predicting mortality.
Elshazli R et al (2020)	6,320	Meta-analysis	ICU admission had greater increased WBCs and D-dimer and high IL-6, CRP, D-dimer in terms of mortality	Several immunological markers, could be helpful to be included in routine panel for COVID-19.

Jain A et al (2021)	735	Retrospective observational	CRP, D-Dimer and CT severity score levels only can predict final outcome of death.	CRP of 45 mg/l, D-dimer of 1000 µg/L and CT = 15 on admission highly predictive of outcome
Kurri et al (2021)	84	Retrospective, observational	Average CTSS was 12.43 ± 5.7 Mean D-dimer was 2.5 ± 1.43 in the survivor group and 3.39 ± 0.95 for non-survivors.	The disease severity was significantly correlated with NLR, ferritin, IL-6, D-dimer, CRP, CTSS and D- dimer.
Zhu B et al (2021)	163	Retrospective observational	Significant association between WBC count and death (HR = 5.72, 95%CI: 2.21–14.82, p < 0.001)	WBC count at admission is significantly corelated with death in COVID-19 patients.
Henry BM et al (2020)	2984	Meta-analysis	Biomarkers of inflammation were also significantly elevated in patients with both severe and fatal COVID-19.	Clinicians to closely monitor TLC, platelet count, IL-6 and ferritin as markers for progression to critical illness.
Li J et al (2020)	2445	Meta-analysis	Significant differences between non-severe (non-ICU) patients, severe (ICU) disease in raised TLC, CRP and PCT.	Assessment of inflammatory markers help improve the prognosis of patients with severe illness.
Li Y et al (2020)	140	Retrospective observational	There were significantly differences in CRP, TLC, and NLR between mild/common and severe/critical illness.	CRP may have good independent predictive ability for the development of severe/critical illness
Ata Y et al (2021)	242	Retrospective observational	The CRP (R=0.545, P<0.001) and ferritin (R=0.481, P<0.001) were moderately and positively correlated with CTSS.	Elevation in CRP and ferritin values upon admission to the hospital was significantly correlated with CTSS.
Laguna-Goya R et al (2020)	611	Prospective cohort	High IL-6 level, CRP level, LDH level, ferritin level, d-dimer level, and NLR were all predictive of mortality (AUROC	Inflammatory markers allow early risk stratification of hospitalized patients with COVID-19 before the

			>0.70)	appearance

Asghar MS et al quoted that the laboratory values in non-survivors had lower haemoglobin (Hb) (p=0.016), significantly increased total leucocyte count (TLC) (p<0.001), increased D-dimer levels (p=0.043), and increased procalcitonin (PCT) (p=0.021).[13] *Elshazli R et al* reported that ICU admission was associated with higher levels of TLC, neutrophils, D-dimer, and prolonged PT; patients with high interleukin-6 (IL-6), C-reactive protein level (CRP), D-dimer, and neutrophils had the greatest likelihood of mortality. [14] *Jain A et al* quoted that CRP, D-Dimer and CT severity score levels can predict the final outcome of mortality.[15] *Kurri et al* quoted that for those who survived, the average CT (Computed tomography) severity score (CTSS) was noted to be 12.43 ± 5.7 and whereas average the CTSS for those who did not survive was 18.87 ± 4.68(p<0001); The average D-dimer was noted to be 2.5 ± 1.43 in the survivor group and 3.39 ± 0.95 for non-survivors (p=0.004). They also observed that the correlation coefficient for the CTSS with FiO2 was 0.685 (p<0.0001). [16] *Zhu B et al* quoted WBC count on admission is significantly corelated with mortality in COVID-19 patients and that a increased level of TLC (≥ 6.16 × 10^9/L) should be given more focus in treatment of COVID-19. [17] *Henry BM et al* quoted that patients with fatal and severe disease had significantly greater TLCs, markers of inflammation were also significantly increased in patients with both fatal and severe COVID-19. [18] *Li J et al* quoted that there were significant differences observed in TLC, CRP and PCT amongst non-severe (non-ICU) patients and severe (ICU) disease patients. [19] *Li Y et al* quoted that there were significant differences observed in the CRP (mg/L): 7.3 (2.3, 21.0) vs. 40.1 (18.8, 62.6), TLC:(×109/L): 1.3 (1.0, 1.8) vs. 0.8 (0.7, 1.1), the NLR: 2.1 (1.6, 3.0) vs. 3.1 (2.2, 8.8) between mild/common and severe/critical illness respectively. [20] *Ata Y et al* quoted the CRP and ferritin hade moderate and positive correlation with CTSS, while NLR and ESR had mild and positive correlation with CTSS. [21] *Laguna-Goya R et al* quoted greater IL-6 level, CRP level, LDH level, ferritin level, D-dimer level, and neutrophil-to-lymphocyte ratio were highly predictive of mortality. [22]

In the present study, it was observed that after adjusting for age, gender, CT severity score, ferritin, haemoglobin, TLC, D-dimer, CRP level and NLR, severe ARDS, (i.e: P/F ratio of ≤100) had around 22 times higher chances of having death as an outcome in comparison to those without ARDS (i.e: P/F ratio of >300) (OR: 22.586; p=0.002; C.I: 3.110-164.015). The PaO2/FiO2 ratio was identified as an independent risk factor (odd ratio [OR] = 0.992, 95% confidence interval [CI]: 0.986–0.998, p = 0.006). The area under curve of the receiver operator characteristic (AUROC) of PaO2/FiO2 with mortality as outcome was 0.795 (95% CI: 0.684–0.906, p < 0.0001) with a sensitivity of 80.8% and a specificity of 69.6% when the cut-off value was 226 mmHg. Similar to the findings of this study, *Gu Y et al* reported that the oxygenation index (PaO2/FiO2) was found to be an independent risk factor (odd ratio [OR] = 0.96, 95% confidence interval [CI]: 0.928–0.994, p = 0.021) for mortality. The area under the curve (AUC) was 0.895 (95% CI: 0.826–0.943, p < 0.0001). [23]

This study has several limitations. The sample size was small in this single-centre retrospective study and it is a retrospective study and not a prospective study; hence, the results need to be validated with additional studies. Pharmacological

therapies implemented and the time of hospitalization may affect the laboratory values and PaO2/FiO2. We hence selected the laboratory findings on the day of admission.

Conclusion

In conclusion we observed that age, inflammatory markers (D-dimer, serum ferritin, CRP levels), low haemoglobin (Hb), total leucocyte count (TLC), neutrophil-lymphocyte ratio (NLR), PaO2/FiO2 ratio and chest CT severity score (CTSS) show significant correlation with the outcome of the patient. PaO2/FiO2 ratio can potentially be used as an independent risk factors for predicting mortality in COVID-19 patients requiring intensive care. Thus, clinicians can consider the inflammatory markers and PaO2/FiO2 ratio in particular and take active steps required to reduce the mortality from COVID-19.

Conflict of interest: None
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