

Comparative Study of Hematological Parameters of Covid Positive Patients In ICU Requiring Oxygen With Or Without Ventilatory Support

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Background and aims: The ongoing Covid pandemic has burdened the medical system, more so due to the limited availability of ventilators. Our study aims at identifying the role of hematological markers in the risk stratification and the need for ventilator support among ICU admitted COVID-19 patients.

Methods: A single centre prospective study was conducted on 100 Covid positive patients admitted in the ICU to determine association between the haematological markers such as-Hb, Platelet count, Total and Differential leukocyte count, CRP, AST, ALT, LDH, Ferritin and D-Dimer with the need for oxygen therapy with or without invasive ventilatory support. Comparative analysis was performed between the 2 groups.

Results: Neutrophilia, a mean of 76.7% among those ventilated and 71.6% among those non ventilated (p value 0.002; highly significant) and Lymphocytopenia (p value 0.004) with a mean of 14% and 18.6% respectively was noted. Hemoglobin levels were lower in ventilated (mean 11.6g/dl) as against those non ventilated (mean 12.58%) p value 0.046 which was significant. D-dimer was increased in COVID-19 patients; mean 5380 ng/ml in ventilated patients and mean 949ng/ml in those non ventilated ($P < 0.001$ highly significant). Elevated D-dimer and presence of diabetes correlated with increased chances of mechanical ventilation, while higher hemoglobin levels and associated COPD have a negative association with the need of mechanical ventilation.

Conclusion: Hypercoagulability along with neutrophilia and lymphocytopenia can be used as positive associations for the need for invasive mechanical ventilation.

Keywords: Covid, Hematological parameters, Mechanical ventilation.

Introduction

SARS-CoV-2 is responsible for the recent COVID-19 pandemic and has affected 1,99,25,604 people in India with 2,18,959 succumbing to this disease and 8944 critical patients as of September, 2021¹; and this number is only increasing as this article is being written. It heralds an inflammatory response causing recruitment of macrophages and monocytes with cellular destruction, release of cytokines and chemokines which results in activation of the immune system.^{2,3} Severe infection

has been reported in those with elevated levels of serum ferritin, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and interleukin-6 (IL-6)^{4,5} However, other studies have observed no difference in these levels, making these markers controversial.^{6,7,8} Thus, predisposing factors or hematological markers which can effectively predict the severity of the disease or the need for mechanical ventilation are not clear. 5-15% of patients with COVID-19 require observation in the intensive care unit (ICU), with ventilatory support⁹ In a country as vast as India and with limited availability of ventilators, the healthcare system is challenged with increasing number of cases. Considering the evidence which proves that lung protective ventilation improves the clinical outcome of patients with ARDS, it is imperative that ventilators be used appropriately¹⁰ Limited resources in low-income countries drive researchers to investigate predictive blood parameters to categorize and mobilize patients at risk of requiring invasive ventilation, to appropriate centers. Our study was aimed at identifying the role

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of hematological markers of inflammation in the risk stratification for the need for mechanical ventilation among COVID-19 patients in ICU.

Methodology:

A prospective observational study was conducted in 100 covid positive patients admitted in the ICU of Father Muller Medical College Hospital over a period of 4 months by purposive sampling method. All patients admitted to ICU with positive real time reverse transcriptase polymerase chain reaction were included in the study. Among them were patients requiring oxygen therapy via venturi device, non-rebreathing bag mask, high flow nasal oxygen or invasive mechanical ventilation. All recruits were between 18 years and 80 years old. Medical records were reviewed to collect information on demographics, presenting complaints, duration of onset of symptoms, and for the presence of associated comorbidities. Results of the following inflammatory markers collected at the time of admission were noted; white blood cell count, lymphocyte count ($\times 10^9/L$), neutrophil granulocyte count ($\times 10^9/L$), CRP level (in milligrams per liter), lactate dehydrogenase level (in IU/L), Ferritin, D-dimer, Liver enzymes. Subsequent laboratory tests were not considered. The criteria used to admit covid positive patients from the casualty to ICU were evidence of respiratory distress recognized clinically by decreased oxygen saturation measured on pulse-oximeter ($SpO_2 < 70-75\%$), increase in respiratory rate with evidence of increased work of breathing-use of accessory muscles of respiration (respiratory rate > 20 breaths/min) and with chest X-ray revealing features of ARDS. Following admission to ICU, patients were categorized as mild/moderate/severe Covid based on HRCT.

Mild and moderate diseased patients were started on venturi 0.6 with oxygen at 15L/min. If patient had improving respiratory parameters and improvement in chest X-ray over the course of treatment with good oxygenation in ABG, FiO_2 and flows were tapered. Those with $SpO_2 < 90\%$, $RR > 35/min$ were switched to NRBM. Patients with moderate disease in whom oxygenation was impaired on NRBM (complaints of dyspnoea, $SpO_2 < 90\%$, $RR > 35/min$, $PaO_2 < 60$ on ABG) were treated with HFNO with FiO_2 0.6, flow of 40L/min to a maximum of 60/L, FiO_2 0.9.

Patients with severe Covid as evidenced by respiratory distress on HFNO ($RR > 35$, $SpO_2 < 90\%$, $PaO_2 < 60$ on ABG) were mechanically ventilated with cuffed endotracheal tube with IPPV, following the institutional ARDS protocol (low tidal volume, high respiratory rate to maintain $P_{plat} \leq 30$ starting with PEEP of 14, with infusion of intravenous sedation, muscle relaxation as per co morbid conditions and body weight for 2 days. Ventilator settings were tapered as per improvement in PaO_2 , chest Xray and SpO_2 .

Comparison of the hematological markers of inflammation among those who required mechanical ventilation and not were performed by Mann Whitney test. Optimal cut off was obtained by ROC. Logistic regression analysis was performed for those variables which were found significant in the univariate analysis.

Results:

100 Covid positive patients admitted in the ICU of Father Muller Medical College were recruited. 65% were male and 35% female. 64 patients required mechanical ventilation and 39 of them succumbed to the death. 36 did not require mechanical ventilation.

Table 1: Age of the patients

	<25yrs	25-50yrs	50-75yrs	>75yrs
Male	1	19	38	7
Female	4	6	19	6
Total	5	25	57	13
Ventilated	1	16	38	9
Not ventilated	4	9	19	4
Total	5	25	57	13

Table 1 shows the age distribution of the cohort and requirement of mechanical ventilation depending

on the age factor. It was noted that the maximum number of patients both affected with Covid and

requiring ventilator support were in the age group 50-75yrs. The mean age of those ventilated was 57.82 and those not requiring ventilation was 55.16. Table 2 shows the presence of co-morbidities and their distribution among ventilated and non-ventilated patients. Table 3 shows the laboratory profile on admission and their comparison between ventilated and non-ventilated patients. Neutrophilia, lymphocytopenia and increased D-

Dimer levels were associated with in requiring ventilatory support in COVID-19 patients with a sensitivity of 78%, 100% and 100% respectively. Table 4 shows the results of logistic regression analysis of the parameters. During the analysis done on the significant parameters, D-dimer levels, haemoglobin and co-morbidities like diabetes and COPD were found to have a positive correlation.

Table 2: Co-morbidities of patients

	NOT VENTILATED		VENTILATED		P value
	COUNT	ROW N%	COUNT	ROW N%	
HTN	13	26.5%	36	73.5%	0.053
Diabetes	12	23.5%	39	76.5%	0.008
AKI	2	12.5%	14	87.5%	0.033
COPD	7	87.5% ¹		12.5%	0.002
CVA	0	0	4	100%	0.126
IHD	8	38.1%	13	61.9%	0.822
CKD	4	22.2%	14	77.8%	0.179
RHD+AF	0	0	2	100%	0.284
Asthma	3	37.5%	5	62.5%	0.927
Carcinoma	1	33.3%	2	66.7%	0.922
Hypothyroid	2	33.3%	4	66.7%	0.888
Chronic liver disease	0	0	5	100%	0.085

Table 3: Hematological Parameters

	Ventilated (n=64)		Non ventilated (n=36)		P VALUE	
	MEAN	SD	MEAN	SD		
D Dimer	5380.19	12225.23	949.86	971.63	0.001	Highly significant
Neutrophil	76.70	15.85	71.67	9.26	0.002	
Lymphocyte	14.09	9.43	18.61	7.98	0.004	
Basophil	5.48	2.97	6.69	2.89	0.045	Significant
Eosinophil	1.41	1.53	2.47	2.76	0.021	
Hemoglobin	11.69	2.20	12.58	2.47	0.046	
Total Count	9290.94	4177.95	8400	3446.57	0.373	Not significant
PCV	2.53	1.23	2.16	0.92	0.243	
CRP	271.73	199.21	284.39	391.01	0.115	
Ferritin	1142.45	1682.90	1512.47	2716.72	0.625	
LDH	362.48	230.33	466.50	376.31	0.194	
AST	59.20	58.52	62.03	71.34	1.000	
ALT	39.89	28.48	39.67	28.68	0.997	

Table 4: Logistic Regression Analysis

Variables in the Equation									
	B	S.E.	Wald	Df	p	odds ratio	95% C.I. for odds ratio		
							Lower	Upper	
D DIMER	.000	.000	4.176	1	.041	1.000	1.000	1.001	
HB	-.281	.136	4.269	1	.039	.755	.578	.986	
DM(1)	1.389	.574	5.859	1	.015	4.011	1.303	12.354	
COPD(1)	-3.015	1.209	6.223	1	.013	.049	.005	.524	
N	-.029	.042	.482	1	.488	.971	.895	1.054	
L	-.056	.051	1.210	1	.271	.945	.856	1.045	
B	-.083	.102	.661	1	.416	.920	.753	1.125	
E	-.277	.159	3.052	1	.081	.758	.556	1.034	
AKI(1)	1.271	.916	1.925	1	.165	3.564	.592	21.470	
Constant	6.919	4.813	2.066	1	.151	1011.497			

Elevated D-dimer levels (OR=1 ,95% CI 1-1.001) and presence of diabetes (OR=4.011 ,95% CI 1.303-12.354) was associated with patients requiring mechanical ventilation. An elevated hemoglobin (OR=0.755 ,95% CI 0.578-0.986) and presence of COPD (OR=0.049 ,95% CI 0.005-0.524) have an association with reduced need for mechanical ventilation.

Discussion:

Several studies showed similar outcomes with respect to age distribution and male predominance in COVID-19 as our study.¹¹⁻¹⁵ A large number of patients affected by the disease had multiple comorbidities indicating a correlation with disease severity¹⁴⁻¹⁷ and an increased likelihood for requiring ventilator support. In a study by Hansen et al¹⁶ on the risk of severe outcomes among Covid patients with asthma and COPD, age standardized difference showed no significant difference. Our study demonstrated negative association between COPD and Covid positivity with respect to need for mechanical ventilation. The probable reason being that exacerbations in COPD are associated with high levels of Type 2 inflammation¹⁷, while in Covid 19 infection type 2 inflammation has been suggested to protect against adverse outcomes.¹⁸ However, protective value of COPD as a comorbidity in Covid positive patients cannot be inferred due to the fact that limited population was analyzed in the study.

A prospective observational study done by Muhammed S Asghar¹¹ comparing the role of biomarkers in the survivors, on invasive vs

noninvasive ventilation, concluded that 39% of the subjects did not need respiratory support, while 13% were on a ventilator, 16% on bilevel positive airway pressure/continuous positive airway pressure, and 31% on supplemental oxygen therapy. In our study, 56% were directly put on mechanical ventilation and 44% were initially started on oxygen therapy with venturi. Out of the 44 patients on venturi, 50% required NRBM, out of which 72.7% (16 patients) required HFNO, out of which 9 (56.25%) required mechanical invasive ventilation. Bi valve positive airway pressure and CPAP was not used as the initial mode of ventilation in our hospital. It is only used at the time of weaning. The hematological and immunological parameters have shown a similar trend in most studies.^{11,14,15} Laboratory findings detected in the majority of COVID-19 patients includes lymphocytopenia (82.3%), thrombocytopenia (36.2%) and leukopenia (33.7%) Majority of patients reported high levels of CRP and less frequently high levels of ALT,AST and D-dimer levels. We limited our study to analyze the difference in hematological and immunological parameters which could help in predicting the need for invasive mechanical ventilation. We noticed that neutrophilia, lymphocytopenia and elevated total leukocyte counts were detected in the ventilated group. These findings are consistent with other studies^{11,19-21} We did not note any significant change in platelet levels and its association with mechanical ventilation. The similar finding was observed in a study conducted by Muhammed et

al¹¹ However, Yang *et al*²⁰ noted significant thrombocytopenia in patients with severe disease. Elevated levels of inflammatory parameters CRP, LDH, D-dimer, erythrocyte sedimentation rate (ESR), ferritin and procalcitonin (PCT) were noted, also seen in multiple studies¹⁹⁻²¹

Our study had a few limitations. The sample size was relatively small as compared to other studies. We did not use follow-up parameters to assess variation with disease progression.

Based on the findings of our study, the management plan can be tailored at any stage of the disease provided a set of hematological markers are

obtained on appearance of symptoms and its trend with symptom progression is correlated and ventilator strategy escalated and de-escalated accordingly.

Conclusion:

Lymphocytopenia and neutrophilia can be used as an initial marker to identify those who might require invasive ventilation. Based on our findings, it is noted that COVID-19 patients had hypercoagulability and that plasma D-Dimer might guide in the decision making.

High levels of Ferritin, LDH and CRP were noted in positive patients.

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