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Comparison of Haematological Parameters Of Critically Ill Survived & Non Survived COVID-19 Patients

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Abstract

This is a retrospective case series to determine the hematological parameters of ICU admitted COVID-19 patients conducted in tertiary care Hospital.

Heart Rate was seen to be significantly increased (p value 0.037) in non-survived (94.77 ± 14.96) patients compared to the survived patients (94.77 ± 14.96). Significance (p value <0.0001) is observed as the WBC count of non-survived (11393.37 ± 6212.11/cmm) which is more than that of survived (8060.45 ± 3932.25 /cmm). Mean of differential neutrophils count was significantly (p <0.0001) higher in non-survived patients (83.95%) compared to survived patients (78.27%). Mean differential lymphocyte count in survivors is (16.19%) compared to (10.21%) in non survivors; a significant (p<0.0001) lymphopenia was observed in non survivors. Statistical significance (p <0.0001) is observed in LDH of non- survived (667.40 ± 664.65 U/L) which is more than that of survived (419.14 ± 172.78 U/L). C-reactive protein (CRP) of survived (52.54 ± 26.39 mg/L) is significantly (p<0.0001) more than that of non- survived (27.11 ± 32.87 mg/L). SGOT in non-survived (124.05 ± 520.03 U/L) is significantly (p=0.013) higher compares to that in survived (52.43 ± 31.92 U/L) in survived. Creatinine of non-survived (1.60 ± 1.15) is significantly (p<0.0001) more than that of survived (1.51 ± 3.11).

Leucocytosis, Lymphopenia and Neutrophilia are observed significantly more in non survivors and may account for poor prognosis. Increased inflammatory markers exhibit the possibility of progression of COVID-19 infection towards severity. Haematological parameters are immense functional value for the primary prognostic appraisal of patients with fatal COVID-19 infection.

Keywords: COVID-19, Haematological, Non-survived

Introduction

Pathogen isolated from the respiratory samples of patients with pneumonia of unknown aetiology in Wuhan epicentre was given the acronym of 2019-nCoV by World Health Organization (WHO) [1]. It was later renamed by Coronavirus Study Group of International Committee on Taxonomy of Viruses as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) as it has strong phylogenetic homogeneity with SARS-CoV-1 of the same subgenus.First patient of COVID-19 in India was discovered from Kerala on January 30th, 2020 [2].

COVID-19 disease has comprehensive clinical indications varying from asymptomatic carrier state or mild pneumonia to respiratory distress or multiple organ failure requiring intensive care admission [3]. Recent corroborations suggest that SARS-CoV-2 might providentially disrupt normal functions of the kidney, liver and peripheral blood components, thus increasing the risk of multiple organ failure [4,5,6]. Inflammatory response which is favourable for thrombosis is highly increased in COVID-19 infection. High levels of C-reactive protein (CRP), D-dimer, albumin, ferritin and LDH levels are the indirect indicators are proven to be important in estimation of COVID-19 infection severity[7,8].

Hemocytometric changes can be considered as probable indicators to estimate disease severity and also provides supporting evidence of a COVID-19

infection according to various international guidelines. Lymphopenia and Neutrophilia were considered as prognostic markers for severe COVID-19 cases as per guidelines for Australia and New Zealand released in March 2020 [10].Lymphopenia (63%), leucocytosis (24–30%) and leukopenia (9–25%) were among the most common laboratory irregularities in hospitalized patients COVID-19 pneumonia reported by the Centers for Disease Control and Prevention of United States [11].

Almost all the clinical laboratories are equipped with haematology analyser, required for performing the most commonly done haematological laboratory test of Complete Blood Count and providing its result promptly. It would be obliging to emphasize on parameters that are widely available and economical to ensure that they can be widely implemented.Symptomatic supportive treatment, prevention of secondary infection and prompt organ function support are of paramount importance to reduce complications and mortality in severe cases.

Aim: To compare the Haematological parameters of critically ill Survived & Non-survived COVID-19 patients admitted at Tertiary Care Hospital of Central India.

Objectives:

To compare haematological parameters of critically ill Survived & Non Survived COVID-19 patients

To assess whether these haematological parameters are of any prognostic value.

Materials And Methods:

Study Design: This is a retrospective observational study of 206 critically ill COVID-19 patients conducted in MGM Medical College & Hospital, Aurangabad, Maharashtra; during 1st January 2021 to 31st May 2021. Purposive sampling was used to select cases and all confirmed cases with positive reverse transcription-polymerase chain reaction (RT-PCR) for SARS-CoV-2 virus that were critically ill & required ICU admission at MGM tertiary care hospital of Aurangabad, Maharashtra. ICU COVID-19 patients who were less than 18 years of age at the time of admission or patients who stayed for less than 24 hours in the ICU, pregnant COVID-19 patients and patients who died due to reasons other than complications associated with COVID-19 were excluded.

Approval for the study was obtained from the Institutional Ethical Committee of MGM Medical College and Hospital, Aurangabad, Maharashtra.

Data Collection: All the medical records of included patients were reviewed, collected and evaluated by three researchers. Data consisting of demographic profile, Clinical Electronic Medical records were reviewed regarding Haemogram (Hb%, WBC Count, RBC Count, PCV, MCV, MCH, MCHC, absolute neutrophils and lymphocyte count and Platelet count), Coagulation markers (PT, INR, Ferritin, D-Dimer), Inflammation markers (LDH, CRP, ESR, IL6), LFT (Total Bilirubin, Direct and Indirect Bilirubin, SGOT, SGPT, ALP), RFT (Blood urea, Creatinine) and Serum Electrolytes (Serum Sodium and Potassium).

Statistical Analysis: Data was compiled in MS-EXCEL Sheet and for analysis of this data SPSS (Statistical package for social sciences) Version 20th was used. Continuous variables with normal distribution were presented as mean (Standard Deviation [SD]) and compared between survived & non survived groups by using Student's t –tests. A two sided p value of less than 0.05 was considered to be statistically significant. Categorical Variables were presented as frequency (percentage [%]) & assessed using Pearson χ^2 .

Observations & Results:

Out of the 206 Critically Ill patients, majority were males [149 (72.33)] belonging to the age group of 51-60 years. Mean ICU stay of critically ill patients in our study was 8.24 days. There were minimum patients from the rural area [37 (17.69)]. Majority of critically ill non survived patients were older males and also the residents of urban area.

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Table 1 : Haemogram of Covid-19 ICU Patients

Haemogram	Survived [N=103]	Non Survived [N=103]	Total [N=206]	P-Value
HB (gm. %) 11 - 14 gm.%	12.51 ± 2.02	12.64 ± 1.88	12.58 ± 1.95	0.933
White Blood Cell (WBC) Count (/cmm) 5000 -15000 /cmm	8060.45 ± 3932.25	11393.37 ± 6212.11	9726.91 ± 5072.18	<0.0001
Red Blood Cell (RBC) Count (million/cmm) 4 -5.2 million/cmm	4.62 ± 0.70	4.52 ± 0.67	4.57 ± 0.68	0.17
PCV (%) 34 -40 %	37.70 ± 5.54	37.34 ± 5.37	37.52 ± 5.46	0.38
MCV (fl) 75 -87 fl	81.25 ± 10.38	83.11 ± 7.59	82.18 ± 8.98	0.223
MCH (pg) 24 - 30 pg	27.33 ± 2.94	27.68 ± 3.20	27.50 ± 3.07	0.246
MCHC (g/dl) 31 -37 g/dl	33.49 ± 1.72	33.26 ± 1.73	33.38 ± 1.73	0.911
Differential Neutrophils Count (%) 15 - 80 %	78.27 ± 9.29	83.95 ± 8.73	81.11 ± 9.01	<0.0001
Differential Lymphocyte Count (%) 60 - 80 %	16.19 ± 8.35	10.21 ± 5.66	13.20 ± 7	<0.0001
Platelet Count (1000/Cmm) 200 - 400 1000/Cmm	247.28 ± 113.52	233.88 ± 98.65	240.58 ± 106.09	0.549

In our study, statistical significance (p value <0.0001) is observed as the WBC count of non- survived (11393.37 ± 6212.11/cmm) which is more than that of survived (8060.45 ± 3932.25/cmm). Mean of absolute neutrophils count was significantly (p value <0.0001) higher in non-survived patients (83.95%) compared to survived patients (78.27%). Neutrophilia was significantly more common in non-survived individuals. Mean absolute lymphocyte count in survivors is (16.19%) compared to (10.21%) in non survivors; a significant (p<0.0001) lymphopenia was observed in non survivors. There was no statistically significant difference was observed in platelet count in survivors and non survivors (p value 0.549).

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Table 2: Coagulation Profile Of Covid 19 ICU Patients

Coagulation Study	Survived [N=103]	Non Survived [N=103]	Total [N=206]	P-value
Prothrombin Time (sec) 11 -16 sec	13.33 ± 0.64	13.35 ± 1.42	13.34 ± 1.03	0.384
INR (sec)	1.12 ± 0.06	1.09 ± 0.13	1.10 ± 0.09	0.760
Ferritin (ng/mL) 6 -159 ng/mL	544.96± 634.28	579.56 ± 572.92	562.26 ± 581.10	0.337
D-Dimer (mg/L)	1.49 ± 2.01	1.86 ± 2.41	1.68 ± 2.21	0.041

There was no significant difference observed among the survivors and non survivors in the values of coagulation markers like Ferritin (p value 0.337) or D Dimer (p value 0.041).

Table 3 : Inflammation Markers In Covid 19 ICU Patients

Inflammation Markers	Survived [N=103]	Non Survived [N=103]	Total [N=206]	P-value
Lactate Dehydrogenase [LDH] (U/L) 120-246 U/L	419.14± 172.78	667.40 ± 664.65	543.27± 418.72	<0.0001
C-Reactive Protein (mg/L) <10 mg/L	52.54 ± 26.39	27.11 ± 32.87	39.83 ± 29.63	<0.0001
IL6 (pg/ml) 0 - 6.4 pg/ml	114.63± 171.15	264.73 ± 361.71	189.68± 266.43	0.080
ESR (mm/hr) 0 - 20 mm/hr	27.02 ± 10.87	25.93 ± 10.38	26.47 ± 10.62	0.666

In our study, statistical significance (p value <0.0001) is observed as the LDH of non- survived (667.40 ± 664.65 U/L) is more than that of survive (419.14 ± 172.78 U/L). C - reactive protein (CRP) of survived (52.54 ± 26.39 mg/L) is more than that of non- survived (27.11 ± 32.87 mg/L) which is of statistical significance (p value <0.0001).

Table 4 : Liver Function Test Of Covid 19 ICU Patients

Liver Function Test (LFT)	Survived [N=103]	Non Survived [N=103]	Total [N=206]	P-value
Total Bilirubin (mg%) 0.2 - 1.3 mg%	0.87 ± 1.07	1.09 ± 1.49	0.98 ± 1.28	0.130
Direct Bilirubin (mg%) 0 -0.3 mg%	0.42 ± 0.23	0.65 ± 1.14	0.54 ± 0.69	0.578
Indirect Bilirubin (mg/dl) 0-0.8 mg/dl	0.32 ± 0.17	0.44 ± 0.60	0.38 ± 0.39	0.102

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Serum Glutamic Oxaloacetic Transaminase [SGOT] or Aspartate transaminase [AST](U/L) **17 - 59 U/L**	**52.43± 31.92**	**124.05±520.0**	**88.24± 275.98**	**0.013**
Serum Glutamate Pyruvate[SGPT] or Alanine transaminase [ALT] (U/L) 21 -72 U/L	**36.69 ± 20.83**	**77.99 ± 260.67**	**57.34± 140.75**	**0.452**
Alkaline Phosphatase [ALP](U/L) **38 -125 U/L**	**85.79 ± 35.00**	**111.41 ± 70.16**	**98.60 ± 52.58**	**0.081**

In our study, SGOT in non-survived [124.05 ± 520.03 U/L] is higher compares to that in survived [52.43 ± 31.92 U/L] in survived, which is statistically significant (p value0.013). No significant difference is seen in SGPT values of survived and non-survived.

Table 5 : Renal Function Test Of Covid 19 ICU Patients

renal function test (RFT)	**survived [n=100]**	**non survived [n=100]**	**Total [n=200]**	**p-value**
Blood urea (mg/dl) **15 -37 mg/dl**	**40.28 ± 40.03**	**61.47 ± 48.45**	**50.88± 44.24**	**<0.0001**
Creatinine (mg/dl) **0.7 -1.2 mg/dl**	**1.51 ± 3.11**	**1.60 ± 1.15**	**1.56 ± 2.13**	**<0.0001**

In our study, statistical significance (p value <0.0001) is observed as the Blood Urea of non- survived (61.47 ± 48.45 mg/dL) is more than that of survived (40.28 ± 40.03 mg/dL). Creatinine of non-survived (1.60 ± 1.15 mg/dL) is statistically more significant (p value <0.0001) compared tosurvived (1.51 ± 3.11 mg/dL).

Table 6 : Serum Electrolytes Of Covid 19 ICU Patients

Serum Electrolytes	**Survived [N=100]**	**Non Survived [N=100]**	**Total [N=200]**	**P-value**
Serum Sodium(mEq/L)	**135.19 ± 5.00**	**134.73 ± 14.75**	**134.96 ± 9.88**	**0.294**
135 -148 mEq/L				

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Serum Potassium (mEq/L) 3.5 - 5.5 mEq/L	**4.19 ± 4.73**	**0.73 ± 3.92**	**4.46 ± 2.33**	**0.153**

There was no significant difference observed among the survivors and non survivors in the values of serum electrolytes like Serum Sodium (p value 0.294) or Serum Potassium (p value 0.153).

Discussion:

SARS-CoV-2 cause severe immune response producing large amount of cytokines including lymphokines as well as the early markers of innate immune response affecting mostly the alveolar type II cells and resulting in alveolar wall damage, thus producing a catastrophic primary viral pneumonia. The level of CXCL10 (or some other innate response cytokine) may be predictive of further clinical course [12]. The virus can lead to exaggerated inflammatory response known as cytokine storm characterized by increased interleukin (IL)-2, IL-7, granulocyte colony-stimulating factor (GCSF), interferon-γ inducible protein 10 [13].

In our study, statistical significance (p value <0.0001) is observed in the WBC count of non- survived which is more than that of survived. An overview conducted on 250 hematometric studies of COVID-19 patients in Netherlands indicate that WBC was decreased or normal in COVID-19 patients; however, in severe cases the WBC was increased compared to the non-severe case [13]. Majority of the non-survived critically ill patients in our study were older depicting that mortality increases with increasing age, which is also seen in other studies [14, 15, 16]. Older people are particularly at risk owing to their weakened immunity along with diminished ability of their body to repair the damaged epithelium. A study conducted on 124 elderly COVID-19 patients by Lin et al. showed reduced WBC counts [17]. Zhang et al. conducted a study in which WBC counts were significantly (p = 0.03) higher in the deceased compared to the recovered COVID-19 patients [14].

The differential lymphocyte count in survivors is (16.19 %) compared to (10.21%) in non survivors; a significant (p<0.0001) lymphopenia was observed in non survivors. Consumption of lymphocytes for viral replication results in decreased lymphocyte count accounting for the bad prognosis. A study by Chen et al. shows that percentage of lymphocytes was significantly lower (P<0.05) in the critically severe patients [18]. More severe lymphopenia was seen to be associated with ICU admissions and non-survivors [12]. Mean of differential neutrophils count was significantly (p value <0.0001) higher in non-survived patients (83.95%) compared to survived patients (78.27%). Neutrophilia was significantly more common in non-survived individuals. Similar results were found in a retrospective study on 82 deaths of COVID-19 patients by Zhang et al. resulted that neutrophilia was present in 74.3% of the cases upon admission, and it further increased to 100% in last 24 h before death [19]. Neutrophilia was exhibited in 7 out of the 11 largest studies indicating that neutrophil numbers were mostly normal in non-severe cases but increased in severe infections [13]. The haematological values like WBC count, lymphocytes, neutrophils related to infection were statistically significant in our study similar to previous studies conducted [14, 18, 20].

Hypercoagulability may be the key mechanism for acute organ injury and death in patients with severe COVID-19. In our study, there was significant difference observed among the survivors and non survivors in the values of coagulation markers like D Dimer (p value 0.041). In a large multicentre cohort study of critically ill patients with COVID-19, higher D-dimer levels were independently associated with a greater risk of death [22, 23]. Ferritin levels on admission were three times higher in patients with severe COVID-19 disease compared to patients with less-severe disease [24].

Acute Respiratory Distress Syndrome (ARDS) is the leading rationale responsible for the severity of COVID 19 infection. A study conducted on 113 non-

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survived critically ill patients showed 113(100%) suffered from ARDS [7]. Deadly uncontrolled systemic inflammatory response resulting from the release of large amounts of pro-inflammatory cytokines avowed as cytokine storm is one of the main mechanisms for ARDS [25]. Thus, elevation of inflammatory markers may indicate the possibility of progression to severe disease. In our study, statistical significance (p value <0.0001) is observed where LDH of non- survived is more than that of survived. A pooled analysis of 9 published studies including 1532 patients conducted by Henry et al. resulted that "Elevated LDH levels were associated with a 6-fold increase in odds of developing severe disease and a 16-fold increase in odds of mortality in patients with COVID-19" [26]. A study conducted by Huang et al. in Wuhan, 12 (92%) patients admitted in ICU had LDH levels > 245 U/L [27].

COVID-19 virus directly binds to ACE2 receptors expressed by hepatic cholangiocytes causing deterioration of liver functions that may lead to liver failure and even death. Therefore, liver injury in patients with COVID-19 requires vigilant monitoring. These abnormalities in liver function are presented in the form of abnormal liver profile values. A study by Jiang et al. showed that liver injury developed in 81.5%of the patients in the critically ill group compared with 51.9% in the non-critically ill group; ALT and AST levels were more commonly elevated in critically ill patients ($p < 0.05$) than in the non-critically ill group [15]. In our study, SGOT in non-survived is significantly (p value0.013) higher compared to survived; concluding that non-survived patients tend to have more risk of development of liver injury compared to survived group.

Severe sepsis is a notable cause of mortality leading to multi organ failure and renal failure with acute kidney injury (AKI). A comparative study conducted by Lowe et al. of 81 critically ill patients out of which 36 (44.4%) patients had AKI at any time during their ICU stay [28]. Preliminary study conducted by Yang et al. exhibited that creatinine levels in critically ill group were 76.3 (27.4%) in survived and 80.7 (32.3%) in non-survived[16].In our study, statistical significance (p value <0.0001) is observed as the values of Blood Urea and Serum Creatinine of non- survived is more than that of survived. Abnormal values of renal function test indicate towards high possibilities of development of acute kidney injury.

Conclusion:

High risk group consist of older people in whom there is comparatively more risk of COVID-19 infection leading towards fatal complications. Leucocytosis, Lymphopenia and Neutrophilia are observed more significantly in non survivors and may account for poor prognosis. Increased inflammatory markers exhibit the possibility of progression of COVID-19 infection towards severity. Vigilant monitoring of liver injury by laboratory LFT tests in patients with severe COVID-19 is required as it may proceed to liver failure leading to mortality. Haematological parameters are immense functional value for the primary prognostic appraisal of patients with fatal COVID-19 infection.

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