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Hematological And Biochemical Markers As Risk Factors For Severity Of Covid-19 Infection During 1st And 2nd Wave

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Abstract
Background: The COVID-19 pandemic caused significant disturbance to all aspects of life including health and economy across the world. The mortalities of COVID-19 patients in Pakistan were less than rest of the world.
Objective: This study intends to evaluate Hematological and Biochemical Markers as Risk Factors for Severity of Covid-19 Infection among patients from tertiary care corona dedicated hospitals in Lahore, Pakistan from covid wave 1 to 2 Feb. 26, 2020 to March 31, 2021.
Methodology: The principal investigator along with his team has access on all data collected. total 543 patients were included in current study analysis out which 260 and 283 patients divided into 2 groups wave 1 and wave 2 respectively and the 52 and 89 were excluded due to incomplete laboratory results during 1st and 2nd wave, respectively.
Results: Only 5 out 166 and 7 out of 164 non-ICU admitted patients were died during 1st wave and 2nd wave respectively. On the other hand, 94 out of 260 patients need for ICU admission and 41(43.62 %) ICU patients died during 1st wave of COVID 19 while 112 out 283 need icu admission and 60(53.57%) died during 2nd wave and overall, the death rate in second wave was high in comparison with first wave. The hemoglobin value, neutrophils, lymphocytes, d-dimer, ferritin level and CRP level were higher among ICU admitted patients as compared to non-ICU patients.
Conclusion: our study results revealed that for severity of COVID-19 infection ICU hospitalization include anemia, elevated neutrophil-to-lymphocyte ratios (> 8), platelet-to-lymphocyte ratios (> 192), and D-dimer level (> 0.9 mg\L) at the time of admission.

Keywords: Hematological, Biochemical, Risk Factors, Severity of Covid-19, Infection

Introduction:
Human corona viruses are widespread positive stranded RNA viruses that were first discovered in the 1960s. Because of its characteristic spiky form under an electron microscope, the name "Coronavirus" originates from the Latin phrase corona, which means "crown" or "halo." There are now seven human-pathogenic CoVs that are known to exist [1]. Moderate to severe upper respiratory illnesses, including recurrent colds, are caused by four of the seven corona viruses. Nevertheless, during the previous 20 years, three novel corona viruses have emerged from animal origins, which have been the cause of fatalities and severe, widespread infections [2].
According to W.H.O. the first epidemic of rigorous acute respiratory syndrome by corona virus (SARS-CoV-1) came out in November 2002 from China and caused 800 deaths among 26 countries. Then came the Middle East respiratory syndrome (MERS), spread from camels. MERS recognized in September 2012 in Arabian Peninsula and continues to cause sporadic and localized bursts. [3]
Globally, over 125 million diagnosed cases of COVID-19 have been reported. Pakistan is walking on a tight rope with rising number of cases and economic restraints.[4] The virus was confirmed to have reached Pakistan on 26th February 2020, when

a student in Karachi tested positive upon returning from Iran. As of 20th June 2020, there have been about 171,700 confirmed patients with 63,500 recoveries and 3,380 deaths in the country. The country was put under a nation-wide lockdown from 23rd of March, until 25th of April 2020 followed by partial & smart lockdowns, though there is dichotomy of opinion at policy level regarding the need of lockdown. [5]
Relative laboratory findings have also been related with poorer prognosis. These include: Lymphopenia, Thrombocytopenia, Deranged liver enzymes, Deranged lactate dehydrogenase (LDH), Deranged inflammatory markers (eg, C-reactive protein [CRP], ferritin) and inflammatory cytokines (ie, interleukin 6 [IL-6] and tumor necrosis factor [TNF]-alpha)., Deranged D-dimer (>1 mcg/mL), Deranged prothrombin time (PT), Deranged troponin, Deranged creatine phosphokinase (CPK) and Acute kidney injury [6].
A systematic analysis of studies assessing the chest CT results in over 2700 infected with COVID-19, the following variations were eminent: Opacifications – 83 %, Opacifications with consolidation – 58 %, adjoining pleural thickening – 52 %, Inter-lobular septal thickening – 48 %, Air broncho-grams – 46 %.[7]

Objective: This study intends to evaluate Hematological and Biochemical Markers as Risk Factors for Severity of Covid-19 Infection among patients from tertiary care corona dedicated hospitals in Lahore, Pakistan from covid wave 1 to 2 Feb. 26, 2020 to March 31, 2021.

Material and method
This research has been carried out as multicenter analytical study based upon primary data of covid 19 admitted patients at corona dedicated centers officially by the govt of Punjab. Lahore is the 2nd largest populated city of Pakistan with a projected residents of 12 million with an annual growth rate of 5.9 %. The duration of this research from Feb. 26, 2020 to March 31, 2021.

Study design:
Hospital based cross sectional analytical component as hypothesis testing among study sub group analysis.
Study duration:
26TH of Feb, 2020 to 31st march 2021.our study data has been collected from study subjects suffering from corona infection wave 1 to wave 3 in the largest metropolitan city of province Punjab, Pakistan

Sample Size:
The principal investigator along his team has access on all data collected under his direct supervision thru well trained data collectors along with collaborative access to the multicenter tertiary care hospitals of Lahore. total 543 patients were included in current study analysis out which 260 and 283 patients divided into 2 groups wave 1 and wave 2 respectively

Sampling Technique:
Non-probability consecutive sampling
Study Settings:
Covid-19 Disease Surveillance and treatment Centers formed in Lahore for isolation and treatment of covid-19 patients, which mainly includes teaching hospitals of Lahore like Mayo hospital, general hospital, services hospital and also isolation center in expo center.

Inclusion Criteria:
1.Lab diagnosed COVID-19 admitted patients
2.Clinical diagnosed COVID-19 with biochemical and radiological abnormalities consistent with COVID-19

Exclusion criteria:
1.Home isolated patients
2.Those patients who left against medical advice
3.Those patients with missing clinical notes

DATA ANALYSIS PLAN:
- We developed objectively structured questionnaire from our study subjects based upon their complete medical history of corona illness comprising of complete lab investigations for their biomarkers, clinical sign and symptoms, associated comorbidities and sequalae.
- Data was entered in SPSS 23.0 and analyzed as per sub group analysis in tabulated format, observed number as frequency and corresponding percentages for the qualitative variable. While mean and standard deviations for the quantitative variables the association of the different variables was calculated thru chi- square for statistical significance.
- P-value < 0.05 to be taken statistically significant

ETHICAL CONSIDERATION:
Study Ethical Review Board approval was obtained from the ERC committee of our institution. Informed verbal consent from the attendants of the all the patient who remained admitted in hospital and died in our hospital center. Confidentiality of the data obtained was maintained throughout the conduct of the study with dissemination of the study results to their families and attendants accordingly.

Results:
The total 86852 COVID 19 confirmed patients with 41126 in first wave and 45726 in second wave were reported according to Government of Pakistan and World meter from District Lahore, Pakistan (Table1). Most of the patients were recovered after COVID 19 especially in second wave exposure. Out of total 86852 patients of both waves, the death of only 1.04 % COVID 19 patients was reported. The test of the population of reasonable size were conducted. Total tests 1,412,125 were performed to screen the population.

Table 1 Status of COVID 19 in Lahore

Sr. No.	Particular	1st Wave	2nd Wave	Total
1	Total Number of Confirmed Patients	41126	45726	86,852
2	Total recoveries	40,714	45,237	85,951
3	Total death	412	489	901
4	Total Cases / million	274	305	579
5	Deaths / million	1.82	2.03	3.86
6	Total tests	568,563	843,562	1,412,125
7	Tests / Million	3,790	5,624	9,414

Source: COVID-19 Government of Pakistan and World meter

In present study, total 312 admitted COVID 19 patients during 1st wave were considered initially. Out of these 312 patients, 52 were excluded due to incomplete laboratory results. Out of the remaining 260 patients, 166 (63.84 %) patients were not shifted in ICU. The 96.99% non-icu patients were recovered and discharged. Only 5 non -icu patients were died during 1st wave. On the other hand, 94 out of 260 studied patients were shifted in ICU. The 43.62 % ICU patients died in Lahore during 1st wave of COVID 19 (Figure 1)

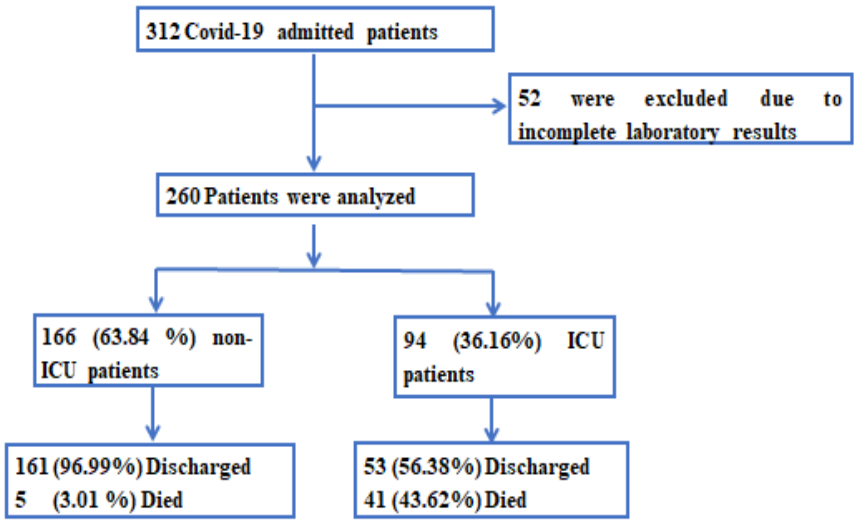

Figure 1: Flow sheet of study participants during 1st wave of COVID 19

In present study, total 372 admitted COVID 19 patients during 1st wave were considered initially. Out of these 372 patients, 89 were excluded due to incomplete laboratory results. Out of the remaining 283 patients, 171 (60.42 %) patients were not shifted in ICU. The 95.91% non ICU patients were recovered and discharged. Only 7 non-ICU patients were died during 2nd wave. On the other hand, 112 out of 283 studied patients were shifted in ICU. The 53.57 % ICU patients died in Lahore during 2nd wave of COVID 19 (Figure 2). Overall, the death rate in second wave was high in comparison with first wave (Figure 4.4). The number of admitted patients in 2nd wave was also high.

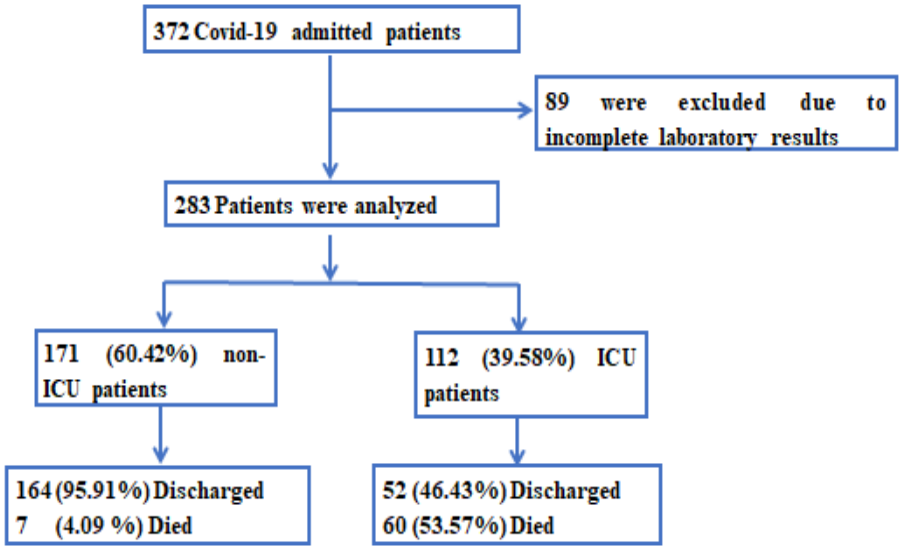

Figure 2: Flow sheet of study participants during 2nd wave of COVID 19

In present study, the hematological parameters of all studied COVID 19 patients were recorded. The hemoglobin level of mostly patients was higher than permissible range. The hemoglobin value, in general, were higher (13.26 and 13.90 g/dl) in non-ICU admitted patients than ICU admitted patients (12.96 and 12.40 g/dl) during 1st and 2nd wave of COVID 19, respectively (Table 2). On the other hand, the reverse trend was observed in ICU admitted patients than non-ICU admitted patients for WBCs. The mean WBCs 11.20 x 10^3/ µl and 12.45 x 10^3/ µl were recorded in ICU admitted patients during 1st and 2nd wave, respectively. The mean neutrophil ranged from 6.22 x 10^3/ µl to 7.17 x 10^3/ µl and from 7.62 x 10^3/ µl to 8.45 x 10^3/ µl in 1st and 2nd wave of non-ICU and ICU admitted patients, respectively. The lymphocytes in non-ICU patients were higher than ICU patients. The platelets in ICU admitted patients were higher than non-ICU admitted patients during both COVI D 19 wave. The highest mean platelets 312 x 10^3/ µl in patients admitted in ICU were recorded (Table 2). The mean NLR values ranged from 16.64 and 17.69 and from 5.14 to 7.53 during 1st and 2nd wave in ICU admitted and non-ICU admitted patients, respectively. Similar trend appeared in PLR and INR in COVID 19 admitted patients (Table 2).

Table 2: Hematological parameters of COVID- 19 admitted patients in District Lahore, Punjab, Pakistan

Particular	Non-ICU patients		Admitted to ICU		P-value
	1st wave (n=166)	2nd wave (n=171)	1st wave (n=94)	2nd wave (n=112)	
Complete blood count (CBC)					
Hemoglobin (g/dl)	13.26±1.23	13.90±1.68	12.96±1.87	12.40±1.56	<0.01
Anemic (HB <12)	50 (30.12)	54 (31.58)	52 (55.32)	64 (57.14)	<0.001
WBCs (10^3/ µl)	8.10±3.75	8.45±4.12	11.20±7.75	12.45±4.96	<0.001
Low (<4)	32(19.28)	35 (20.47)	9 (9.57)	12 (10.71)	<0.001
High (>10)	44 (26.51)	51 (29.82)	53 (56.38)	65 (58.04)	<0.001
Neutrophil (10^3/ µl)	6.22±3.9	7.17±4.2	7.62±6.19	8.45±7.26	<0.001
High (>7)	63 (37.95)	65 (38.01)	64 (68.09)	73 (65.18)	<0.001
Lymphocytes (%)	26.72±13.49	21.25±11.56	14.25±12.64	16.24±13.25	<0.001
Low (<20)	76(45.78)	78 (45.61)	77(81.91)	90 (80.6)	<0.001
Lymphocytes (10^3/ µl)	1.45±0.71	1.53±0.78	1.74±0.68	1.96±1.12	<0.001
Low (<1.5)	91(54.82)	92 (53.80)	78 (82.98)	93 (83.04)	<0.05
Platelets (103/ µl)	271.45±130.51	274.26±114.2	278.51±138.35	312.12±128.23	<0.001
High (>450)	15 (9.04)	16 (9.36)	15 (15.96)	19 (16.96)	<0.001

NLR	**5.14±4.72**	**7.53±5.23**	**16.64±24.51**	**17.69±16.25**	**<0.001**
High (>8)	**20 (12.05)**	**21 (12.28)**	**56 (59.57)**	**69 (61.61)**	**<0.001**
PLR	**234.76±206.41**	**289±129.23**	**421.54±356.75**	**419.87±269.58**	**<0.001**
High (>192)	**72 (43.37)**	**76 (43.86)**	**72 (76.60)**	**83 (74.11)**	**<0.001**
INR	**1.04±0.12**	**1.08±0.46**	**1.14±0.28**	**1.19±0.61**	**<0.01**
High (≥1.1)	**23 (13.86)**	**25 (14.62)**	**37 (39.36)**	**47 (41.96)**	**<0.001**

NLR: neutrophil lymphocytic ratio; PLR: Platelets lymphocytic ratio; INR: international normalized ratio

In present study, the ferritin (ng/ml) values were significantly higher (P<0.001) in ICU admitted patients in comparison with non-ICU patients. The mean value reported maximally up to 1245.25 ng/ml. The minimum mean ferritin value was 491.45 ng/ml. The D-dimer values varied between 1.45 to 2.01 mg/L and 4.82 to 4.78 in 1st and 2nd wave of non-ICU and ICU admitted patients, respectively. The CRP was recorded as 39.90 mg/dl in 1st wave and 47.56 mg/dl in 2nd wave patients of non-ICU. Similarly, the CRP 85.51 mg/dl in 1st wave and 83.45 mg/dl was measured in 2nd wave patients of ICU (Table 3).

Table 3: Biochemical markers of COVID- 19 admitted patients

Particular	**Non-ICU patients**		**Admitted to ICU**		**P-value**
	1st wave (n=166)	**2nd wave (n=171)**	**1st wave (n=94)**	**2nd wave (n=112)**	
Ferritin (ng/ml)	**491.45±608.9**	**523.71±541.2**	**1182.24±1344.**	**1245.25±1345.5**	**<0.001**
High (>440)	**62 (37.35)**	**65 (38.01)**	**71 (75.53)**	**88 (78.57)**	**<0.001**
D-dimer (mg/L)	**1.45±2.45**	**2.01±2.96**	**4.82±7.19**	**4.78±8.12**	**<0.001**
High (>0.9)	**50 (30.12)**	**55 (32.16)**	**69 (73.40)**	**82 (73.12)**	**<0.001**
CRP (mg/dl)	**38.90±58.12**	**47.56±42.56**	**85.51±77.45**	**83.45±79.15**	**<0.001**
High (>23)	**75 (45.18)**	**82 (47.95)**	**83 (88.30)**	**102 (91.07)**	**<0.001**

Discussion:

A wide range of hematological variables have been investigated before as potential prognostic markers for the severity of COVID-19. The association between COVID-19 results and anemia, D-dimer levels, platelet-to-lymphocyte ratio (PLR), neutrophil-to-lymphocyte ratio (NLR), and PLR was investigated [8,9,10]. Their findings demonstrated that individuals with COVID-19 had considerably higher mortality and severity of illness when NLR and PLR were higher.[11] Furthermore, it was shown that a relevant adverse effect in patients with severe COVID-19 was anemia. These findings are consistent with an increasing amount of research demonstrating the usefulness of hematological indicators in COVID19 risk assessment and clinical management. Globally, the number of COVID19 cases is rising quickly, which is having an impact on how well healthcare systems function, particularly in terms of the availability of ICU beds. [12,13,14,15]

The best cut-off value in the current investigation for predicting a severe COVID-19 infection was >8. A statistically significant substantial correlation between neutrophil-lymphocyte ratio>3.1 and in-hospital mortality was observed in a large cohort study conducted on a comparable sample [16,17]. This large range of variations could be explained by the lack of a single, accepted definition for severe COVID-19 infection as well as the numerous outcome measures employed in other investigations. Regarding the usefulness of high baseline NLR in predicting severe COVID infection, there is, nevertheless, consensus. The platelet-to-lymphocyte ratio, which is derived from CBC and may be useful in predicting COVID-19 severity, is another straightforward, affordable, but less frequently utilized approach. According to two recent meta-analyses assessing PLR value in COVID-19 infections, patients with more severe COVID-19 infections had higher PLR levels upon admission [18,19,20].

Furthermore, information regarding the severity and prognosis of the disease may be revealed by the quantity and dynamic changes in platelets during the course of treatment. The afflicted patient's cytokine storms were linked to a noticeably elevated platelet count and longer mean hospitalization days [21]. The patient's PLR, which indicates the intensity of the cytokine storm, may be a special indicator in the monitoring of COVID-19 patients (Qu et al Furthermore, patients with more serious deficits in their liver, kidney, and INR were admitted to the intensive care unit [22]. D-dimer, CRP, and serum ferritin levels all considerably rose (p< 0.001). Multivariate regression analysis, however, revealed that the only significant risk factors linked to a severe COVID19 infection that required ICU hospitalization were high NLR (> 8), PLR (>192), and D-dimer (>0.9mg/l). One of the most important and accessible tests for determining the extent of a COVID19 infection is a complete blood count. Anemia may raise the chance of developing a major case of Covid-19, according to certain theories [23,24].

Conclusion:

In present study, the majority of COVID-19-related deaths in patients were males over 50 with high body mass index (BMI) and long-term health conditions such diabetes, hypertension, and ischemic heart disease. With its multisystem involvement resulting to multisystem outcomes, COVID-19 is a heterogeneous disorder.

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