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Original Article

Internal Medicine Section

Predictors of Mortality in Patients of COVID-19 Pneumonia in Intensive Care Unit: An Observational Study in a Tertiary Care Hospital, Lucknow, India

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ABSTRACT

Introduction: Coronavirus Disease-2019 (COVID-19) is caused by the Severe Acute Respiratory Coronavirus-2 (SARS-CoV-2) which is an enveloped positive-sense single-stranded RNA virus. Initial steps of the infection involve binding of the spike protein (S) of the virus to Angiotensin Converting Enzyme-2 (ACE-2) receptor on the mucosal surfaces of various organs like lungs, kidney, heart, intestine. Pathogenesis of complications are still poorly understood.

Aim: This study was designed to find out the baseline biochemical parameters at the time of admission which may predict outcome in COVID-19 patients.

Materials and Methods: This observational study was conducted in a dedicated COVID-19 hospital, Dr. Ram Manohar Lohia Institute of Medical Sciences (Dr. RMLIMS), Lucknow, Uttar Pradesh, India, from 1st July, 2020 to 30th November, 2020. A total of 109 moderate to severe COVID-19 pneumonia patients who required Intensive Care Unit (ICU) admission, were enrolled. Based on their outcome, patients were divided into two groups: "Survived" and "Expired". Biochemical characteristics of patients were compared among the two groups using univariate and multivariate analysis.

Results: On Univariate analysis Coagulation profile, Prothrombin Time (PT), International Normalised Ratio (INR), Activated Partial Thromboplastin Time (APTT) and D-Dimer values were raised significantly in the expired group. Among other acute phase reactants Lactate Dehydrogenase (LDH), C-Reactive Protein (CRP), Interleukin-6 (IL-6), and Creatinine Phosphokinase-MB (CPKMB) were raised in expired group and this difference was significant statistically too. On Multivariate analysis among all acute phase reactant only IL-6 was increased significantly. All other variables were found to be non significantly associated with mortality, statistically (p-value <0.05).

Conclusion: Baseline biochemical parameters have prognostic values in COVID-19 patients. Raised IL-6 levels can be viewed as an independent predictor of mortality among COVID-19 patients at the time of admission in ICU.

Keywords: Coronavirus disease-2019, D-Dimer, Interleukin-6

INTRODUCTION

Coronavirus Disease-2019 (COVID-19) is caused by a SARS-CoV-2 which is an enveloped positive-sense single-stranded RNA virus. First cluster of similar type of pneumonia cases, later named as COVID-19, were found in Wuhan city in the Hubei Province of China, in December 2019. From China, it spread widely and involved almost all the countries. The World Health Organisation (WHO) declared it a pandemic on 11th March 2020. In India, first case was reported on 30th January, 2020 in Kerala, in a student who had returned from Wuhan city of China. First death in India was reported on 10th March, 2020 from the state of Karnataka in a 76-year-old male who had returned from Saudi Arabia. He had co-morbidities-hypertension, diabetes and asthma. Since then mortalities have been increasing continuously and around 19.86 lacs deaths have occurred world-wide [1] while 1.52 lacs patient have expired in India till 16th January, 2021 [2].

The SARS-CoV-2 virus attaches to mucosal surfaces of various organs like lungs, kidney, heart, intestine by binding of its spike protein to the ACE-2 receptors [3]. Most common organ involved is lungs where it manifests as pneumonia; classified according to respiratory rate and oxygen saturation as mild pneumonia {Respiratory Rate (RR) <24/min and SpO_2 <94%}, moderate pneumonia (RR 24-30/min, SpO_2 94-90%) and severe pneumonia (RR >30/min, SpO_2 <90%) [2]. Around less than 5% patients of COVID-19 get critical illness and complications like Acute Kidney Injury (AKI), myocarditis, Acute Respiratory Distress Syndrome (ARDS) etc., which increases morbidity and mortality in these patients. Risk of mortality increases in severe to critical illness [4]. Pathogenesis of complications are still poorly understood. Many studies have shown downregulation of ACE-2 enzyme which prevents conversion of angiotensin-2 to angiotensin-1. Angiotensin-2 molecule is proinflammatory which leads to inflammation and tissue injury which ultimately leads to complications like myocardial injury, AKI and ARDS etc., [5]. There is no positive association between severity of disease and level of ACE-2 receptors. These receptors are more in males as compared to females and this may be the cause of higher complication rate in male patients [6]. The complications of COVID-19 pneumonia and mortality is largely dependent on age, co-morbidities and severity of disease [3]. Advanced age, elevated Lactate Dehydrogenase (LDH) and D-Dimer are also found to be risk factor for ARDS and mortality [7].

The IL-6 is a cytokine which has multiple mechanisms. It regulates immune cells by transmitting cell signals, it also has strong proinflammatory effect which causes inflammation, tissue injury, ARDS, sepsis, septic shock, multi organ failure and eventually death [8]. Considering the novelty of the disease and health impacts of the COVID-19, this study was an attempt to find out baseline biochemical parameters at the time of admission which may predict poor outcome in COVID-19 patients.

MATERIALS AND METHODS

A prospective observational study was carried out at Dr. Ram Manohar Lohia Institute of Medical Sciences (Dr. RMLIMS), Lucknow,

Uttar Pradesh, India from 1st July, 2020 to 30th November, 2020. The COVID-19 facility at Dr. RMLIMS was a designated Level-3 treatment facility to provide healthcare to moderate to severe COVID-19 pneumonia patients. The Institutional Ethical Clearance was obtained by Ethical Committee (IEC NO.63/20).

Inclusion criteria:

- Patient of moderate (RR 24-30/min, SpO_2 94-90%) to severe COVID-19 pneumonia (RR >30/min, SpO_2 <90%) confirmed by Reverse Transcription-Polymerase Chain Reaction (RT-PCR) and admitted to Intensive Care Unit (ICU) [9].
- Consent to participate in the research study, received either from the patient or attendant.

Exclusion criteria:

- Patient age <18 years
- Patient suffering from other moribund non COVID-19 disease which could cause death of patient like end stage renal disease, terminal cancer, end stage liver disease, pre-existing chronic lung disease etc.,
- Pregnant females.

Study Procedure

All moderate to severe COVID-19 pneumonia patients requiring admission from 1st July, 2020 to 30th November, 2020 were included in the study. A total of 140 patients confirmed by RT-PCR test who required admission in ICU, were recruited for the study and 31 patients had to be excluded as they did not fulfil the inclusion criteria. So, a total of 109 patients were included in the study and their data was analysed. During hospitalisation, patients were treated in ICU with a standard institutional protocol consisting of intravenous Remdesivir, Dexamethasone, Enoxaparin, appropriate antibiotics and other necessary treatment. Patients were given other support like ventilator, dialysis, blood transfusion etc., whenever required.

All eligible patients underwent detailed clinical examination, and relevant investigations such as Complete Blood Count (CBC), Renal and Liver Function Tests (RFT and LFT), Random Blood Sugar (RBS), Serum Ferritin, IL-6, Procalcitonin, PT-INR, APTT, Fibrinogen, D-Dimers. Based on outcome after hospital stay, patients were divided into two groups.

Group 1 (non-survivor or expired)- This group included patients who died during the hospital stay.

Group 2 (survived)- This group included patients who survived during the hospital stay and were discharged after recovery.

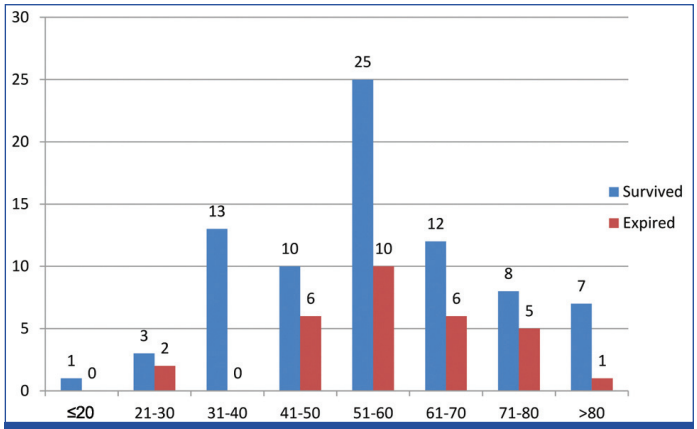
All demographic (age and sex), clinical and laboratory parameters were compared between Survivor and Non survivor groups.

STATISTICAL ANALYSIS

Discrete data were analysed by cross-tables using descriptive method. Continuous data was represented as mean and Standard Deviation (SD). Continuous variables were compared between the two groups using student's t-test. Biochemical characteristics of patients among survived and non survived groups were compared using univariate and multivariate methods. The p-value<0.05 was considered as statistically significant.

RESULTS

A total of 109 moderate to severe COVID-19 pneumonia patients who required ICU care, were enrolled in the research study. Out of 109 patients, 79 patients survived while 30 patients expired during the hospital course. Maximum patients were in the age group of 51-60 years while only one patient was in age group of less than 20 years [Table/Fig-1].



[Table/Fig-1]: Age Distribution of study subjects.

The COVID-19 pneumonia was almost three times more common in males as compared to females. Mean respiratory rate was higher in expired group and mean SpO_2 levels were lower in patients with adverse outcome [Table/Fig-2].

Sr. No.	Variable of interest		Number of patients (n)	Survived	Expired
1	No. of total patients		109	79	30
2	Age (years), mean±SD			56.10±16.567	58.90±13.200
3	Sex	Male	81	63 (77.8%)	18 (22.2%)
		Female	28	16 (57%)	12 (43%)
4	Severity	Moderate	60	59 (98.3%)	1 (1.7%)
		Severe	49	20 (40.8%)	29 (59.2%)
5	Symptoms	Fever	69	48 (69.6%)	21 (30.4%)
		Cough	51	42 (82.3%)	9 (17.7%)
		Breathlessness	63	43 (68.3%)	20 (31.7%)
		Nausea/Vomiting	11	5 (45.5%)	6 (54.5%)
		Myalgia	27	18 (66.7%)	9 (33.3%)
		Common cold	6	6 (100%)	0
		CNS symptoms*	6	3 (50%)	3 (50%)
6	Respiratory rate (per min), mean±SD		109	25.5±6.67	31.5±7.4
7	Systolic BP (mmHg), mean±SD		109	134.94±20.7	132±20.9
8	Diastolic BP (mmHg), mean±SD		109	78.97±12.9	78.6±14.33
9	SpO_2 (%), mean±SD		109	90.5±9.86	86.1±7.75

[Table/Fig-2]: Clinicodemographic data of all patients.
*Giddiness, drowsiness, loss of consciousness

Routine blood investigations were done in both the groups and compared between the two using student's t-test. Mean values of haemoglobin and lymphocyte count were lesser in expired group as compared to survived group. Mean values of Total Leucocyte Counts (TLC), Neutrophilic count, blood urea, AST and Alkaline Phosphatase (ALP) were more in expired group as compared to the survived group [Table/Fig-3].

Acute phase reactants were compared between two groups by Univariate logistic regression analysis. Coagulation profile (PT, INR, and APTT) were raised significantly in expired group while fibrinogen was not changed significantly. Among other acute phase reactants, D-Dimer, LDH, C-CRP, IL-6, and Creatinine Phosphokinase-MB (CPKMB) were raised in expired group and this difference was significant statistically [Table/Fig-4].

All acute phase reactants which were significant in univariate analysis were analysed by multivariate logistic regression analysis. Among all of these acute phase reactants, only IL-6 was increased significantly in expired group as compared to patients who survived. All other variables were non significant statistically [Table/Fig-5].

Sr. No.	Parameters	Survived (Mean±SD)	Expired (Mean±SD)	p-value*
1	Haemoglobin (g/dL)	11.85±2.14	10.12±1.9	**0.001**
2	TLC (10^3 cells/mm^3)	9.67±4.14	13.58±9.02	**0.006**
3	Neutrophils (%)	78.4±13.16	86.621±7.03	**0.002**
4	Lymphocytes (%)	14.91±9.959	7.69±4.2	**0.033**
5	Platelets (10^3 cells/mm^3)	223.8±119.5	206±97.27	0.477
6	Urea (mg/dL)	52.81±43.26	62.5±76.5	0.025
7	Creatinine (mg/dL)	1.25±1.19	1.6±1.45	0.220
8	Sodium (mmol/L)	136.7±6.12	138.6±7.95	0.204
9	Potassium (mmol/L)	4.42±0.67	4.42±1.13	0.987
10	Chloride (mmol/L)	97±10.3	98.63±21.14	0.877
11	Magnesium (mg/dL)	2.87±1.95	2.8±1.91	0.903
12	Phosphorus (mg/dL)	3.37±1.25	3.8±1.4	0.181
13	Total Bilirubin (mg/dL)	0.92±1.54	2.28±1.15	0.197
14	AST (U/L)	66.5±33.6	81.3±51.1	**0.010**
15	ALT (U/L)	49.67±33.9	38.9±24.7	0.146
16	ALP (U/L)	93±43.71	129.8±68.99	**0.005**
17	RBS (mg/dL)	162±72.2	171±54.1	0.631

[Table/Fig-3]: Comparison of lab parameters in two groups.
*p-value <0.05 significant; TLC: Total leukocyte count; AST: Aspartate aminotransferase; ALT: Alanine transaminase; ALP: Alkaline phosphatase; RBS: Random blood sugar

Parameters	Survived (Mean±SD)	Expired (Mean±SD)	OR (95%CI)	p-value
Prothrombin time (seconds)	14.75±2.24	18.15±6.8	0.823 (0.717-0.950)	**0.001**
INR	1.08±0.17	1.37±0.55	0.068 (0.010-0.478)	**0.001**
APTT (seconds)	34.25±7.6	43.0±10.40	0.924 (0.867-0.984)	**0.003**
Fibrinogen (mg/dL)	496.56±199.14	474±160	1.001 (0.998-1.003)	0.647
D-Dimer (µg/mL)	2.58±0.75	4.97±2.98	0.768 (0.656-0.900)	**0.001**
LDH (U/L)	448.76±185.9	617.9±389.4	0.998 (0.996-1.000)	**0.021**
CRP (mg/L)	8.5±6.33	11.96±6.26	0.917 (0.849-0.990)	**0.024**
Ferritin (ng/mL)	603.5±428.8	776.3±423.2	0.999 (0.998-1.000)	**0.092**
IL-6 (pg/mL)	41.91±4.58	105.42±7.175	0.982 (0.971-0.993)	**0.001**
CPKMB (u/L)	23.77±13.9	42.69±30.1	0.955 (0.923-0.989)	**0.001**
Procalcitonin (ng/mL)	0.63±0.52	1.41±0.41	0.895 (0.739-1.083)	0.089

[Table/Fig-4]: Univariate analysis of acute phase reactants.
*p-values based on univariate logistic regression analysis; INR: International normalised ratio; aPTT or APTT: Activated partial thromboplastin time; LDH: Lactate dehydrogenase; CRP: C-reactive protein; IL-6: Interleukin-6; CPK-MB: Creatine phosphokinase-MB

Parameters	OR (95%CI)	p-value
PT (seconds)	18.679 (0.012-2.880)	0.434
INR	0.001 (0.000-1.512)	0.414
APTT (seconds)	0.859 (0.713-1.036)	0.111
D-DIMER (µg/mL)	1.512 (0.619-3.690)	0.364
LDH (U/L)	1.001 (0.994-1.008)	0.707
CRP (mg/L)	0.910 (0.744-1.113)	0.360
IL-6 (pg/mL)	0.972 (0.949-0.996)	**0.023**
CPKMB (u/L)	0.905 (0.786-1.041)	0.160

[Table/Fig-5]: Multivariate analyses of acute phase reactants.
*p-value based on multivariate logistic regression analysis

DISCUSSION

The SARS-CoV-2 virus is a lesser virulent virus as compared to that of other past recent outbreaks like MERS-CoV, Ebola etc. Mortality rate of COVID-19 globally is 2.16% [1], while in India; mortality is lesser, around 1.44 % [2]. Mortality in COVID-19 patients who required ICU care is higher as in present study where it is 27.5%. Mortality rate in ICU patients is reducing over time due to better understanding of the disease and its management. This trend was shown by Dennis JM et al., who showed the change in mortality from 42-19.6% in ICU patients [10].

Acute phase reactants increase in COVID-19 disease, especially in patients who require ICU care. Mechanism of this phenomena is cytokine storm which causes increment in inflammatory markers like LDH, C-reactive Protein CRP, Ferritin, IL-6, Amylase, Lipase etc. Other mechanism is coagulation abnormalities which causes so markers of coagulation abnormalities like PT, INR, APTT, Fibrinogen, D-Dimer etc., also increase. Other markers like CPKMB shows cardiac injury and Procalcitonin shows secondary bacterial infection which leads to morbidity and mortality. All above acute phase reactants were compared in survived and expired group to find out predictor of mortality.

In univariate analysis, among coagulation profile PT, INR, APTT and D-dimer were more elevated in expired group as compared to survived group and this elevation was significant statistically. Other coagulation marker fibrinogen was decreased in expired group but this difference was not significant statistically. Among inflammatory markers, Serum LDH, Serum C-reactive protein, IL-6, and CPKMB were elevated in expired group as compared to survived group. These elevations in markers were significant statistically. Other inflammatory markers like serum ferritin and procalcitonin were also increased in expired group as compared to survived group but this difference was not significant statistically.

All parameters which were significant in univariate analysis were compared by multivariate analysis. Only IL-6 was elevated significantly in expired group as compared to survived group (p-value=0.023). This finding has been supported and refuted by many studies. Trecarichi EM et al., in his study of 50 elderly patients showed higher serum IL-6 levels in expired group and it was identified as an independent predictor of in-hospital mortality. This finding of his study supports our findings [11].

In a prospective, cohort study by Du RH et al., 179 patients were recruited to see predictor of mortality [12]. Only two factors CD3+ CD8+ T cells and cardiac troponin I came as significant predictor while none of acute phase reactants came out as significant predictor of mortality. This was in contrast to our study as we didn't analyse both of factors as predictors of mortality. In a systematic review and meta-analysis done by Tian W et al., authors analysed 4659 patients of 14 studies, they concluded that cardiac troponin, C-reactive protein, IL-6 and D-dimer were predictors of mortality [13]. Similar to these studies, our study also showed IL-6 as predictor of mortality. Others markers like CRP, D-Dimer were also increased in expired group in our study in univariate analysis.

The IL-6 is one of the important markers of cytokine storm so high levels of IL-6 predict severity in COVID-19 patients. Han H et al., enrolled 102 patients and classified them according to severity. IL-6 was significantly elevated in more severe groups which expired later on [14]. Authors concluded IL-6 as a predictor of severity and mortality of disease. Henry BM et al., conducted a meta-analysis with 18 studies and included 2984 patients [15]. They concluded that IL-6 and 10 (IL-10) and serum ferritin were strong predictor of severe and fatal COVID-19 pneumonia.

Liu F et al., studied prognostic value of inflammatory markers in patients with COVID-19 pneumonia [8]. In their retrospective cohort study of 140 patients, they concluded that CRP and IL-6 were independent predictor of severity and outcome of COVID-19 disease. They also suggested IL-6 >32.1 pg/mL as cut-off value which predict severity of disease.

Limitation(s)

This was a single centre study. A multicentric study with a larger sample size was needed to more accurately predict the mortality factors.

CONCLUSION(S)

Biochemical parameters like IL-6 are helpful in predicting mortality in moderate to severe COVID-19 pneumonia patients. IL-6 levels should be routinely measured in all these patients at the time of admission.

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