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Original Article

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A Study of Levels of Il-6 and D-Dimer in Covid 19 Patients and Its Association with Patient Outcome

Dr. Prakash R. Relwani [1], Dr. Ashvinkumar G. Hake [2], Dr. Neelam N. Redkar [3], Dr. Omkar E. Paradkar [4], Dr. Karan R. Desai [5], Dr. Diksha Samsukha [6], Dr. Alhad Mulkalwar [7]

[1]Associate Professor, Department of Medicine, HBT Medical College & Dr RN Cooper Hospital, Mumbai, Maharashtra, India.
[2]Physician, District Hospital, Washim, Maharashtra, India.
[3]Professor and Head of the Department, Department of Medicine, HBT Medical College & Dr RN Cooper Hospital, Mumbai, Maharashtra, India.
[4]Resident, Department of Medicine, HBT Medical College & Dr RN Cooper Hospital, Mumbai, Maharashtra, India.
[5]Resident, Department of Medicine, HBT Medical College & Dr RN Cooper Hospital, Mumbai, Maharashtra, India.
[6]Senior Resident, Department of Medicine, Seth GS Medical College and KEM Hospital, Mumbai, Maharashtra, India.
[7]Tutor, Department of Pharmacology, DY Patil Medical College, Pune, Maharashtra, India.

*Corresponding Author: Prakash Ram Relwani; *alhad.mulkalwar@gmail.com*

Abstract

Introduction: Coronavirus disease 2019 (COVID-19) was declared as a pandemic by the World Health Organization (WHO) in March 20201. COVID-19 severity is linked to cytokine storm driven by IL-6 and elevated D-dimer levels, both indicating inflammation and thrombosis. This study aimed to find the association of level of IL-6 and D- Dimer with clinical outcome in COVID 19 patients. ***Materials and Methods:*** This retrospective, cross-sectional single-centre study analyzed 484 adult COVID-19 patients admitted in a tertiary care centre over a period of one year. It assessed comorbidities, IL-6 and D-dimer levels, and their corelation with outcomes like ICU admission, oxygen need, and mortality. Data were analyzed using OpenEpi, Excel, and SPSS with descriptive stats, chi-square, and correlation tests. ***Results:*** Most common (41.5%) age group involved was 41-60 years with 72.31% males and 27.69% females. Diabetes (50.3%), and hypertension (25.9%), were the most common comorbidities observed. 24.79% had raised D- dimer level and 29.13% patients showed raised IL-6 level. Higher IL-6 (Chi- square =226.0, $p < 0.000001$) and D-Dimer (chi- square = 362.4, $p < 0.00001$) levels were strongly associated with COVID-19 mortality. ***Conclusion:*** Investigations like IL-6 & D Dimer can be useful to assess the prognosis.

Keywords: ***COVID-19, Cytokine Storm, D-dimer, Hospital Mortality, Interleukin-6, Prognosis.***

Introduction

The initial human cases of COVID-19 were identified in Wuhan, Hubei, China. A study in The Lancet published in January 2020 analyzed the first 41 confirmed cases, tracing the earliest symptom onset to December 1, 2019 [2-5]. Human-to-human transmission was officially confirmed by Chinese authorities and the World Health Organization (WHO) on January 20, 2020 [6]. On January 30, the WHO declared COVID-19 a Public Health Emergency of International Concern. By then, the outbreak had grown exponentially-by 100 to 200 times [7]. By July 18, 2020, the WHO reported 13,824,739 confirmed cases and 591,666 deaths globally, with the Americas, Europe, Eastern Mediterranean, and Western Pacific being the most affected regions. In India, there were 1,038,716 confirmed cases and 26,273 deaths, with the most impacted states including Maharashtra, Tamil Nadu, Delhi, Gujarat, Uttar Pradesh, Rajasthan, and West Bengal [8].

Coronaviruses (CoVs) are large, enveloped RNA viruses (80–220 nm) from the Betacoronavirus genus, which also includes SARS-CoV and MERS-CoV. These viruses have a characteristic crown-like appearance due to spike (S) proteins on their surface and contain a large, single-stranded, positive-sense RNA genome (approximately 26–32 kb) [9]. SARS-CoV-2, the virus responsible for COVID-19, mutates rapidly and crosses species barriers, leading to new infections through frequent recombination [10]. It comprises four structural proteins: Spike (S), membrane (M), envelope (E), and nucleocapsid (N) [11]. The spike protein is particularly critical, with S1 binding to host receptors and S2 facilitating membrane fusion. SARS-CoV-2 binds to ACE2 receptors, which are highly expressed in organs such as the lungs, heart, ileum, kidneys, and bladder-especially in lung epithelial cells [12].

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The viral life cycle includes five stages: attachment, penetration, biosynthesis, maturation, and release. After binding to host receptors, the virus enters cells via membrane fusion or endocytosis, replicates RNA and synthesizes proteins, assembles new virions, and releases them to infect other cells.

Symptoms of COVID-19 vary from mild illness to severe respiratory failure and multi-organ damage. CT imaging often reveals ground-glass opacities, even in asymptomatic patients. The virus primarily targets alveolar epithelial cells due to high ACE2 expression, causing early injury in the lungs. Innate immunity in the airways is mediated by epithelial cells, alveolar macrophages, and dendritic cells (DCs), which initiate responses prior to the activation of adaptive immunity [13].

Severely ill patients frequently exhibit elevated levels of proinflammatory cytokines such as IL-6, IL-10, G-CSF, MCP1, MIP-1α, and TNF-α [14]. Although GM-CSF supports immune responses, overproduction may cause tissue damage. High levels of GM-CSF and IFN-γ-producing T cells are seen in autoimmune models and might similarly affect COVID-19 patients, though pediatric responses remain underexplored [15,16]. Endothelial injury may lead to thrombosis and pulmonary embolism, as endothelial cells express ACE2 and play roles in coagulation [17].

IL-6 activates the JAK-STAT pathway, contributing to cytokine storms in severe COVID-19 by causing oxidative stress, abnormal cell proliferation, and impaired viral clearance [18]. D-dimer, a fibrin degradation product, is a biomarker for thrombosis and COVID-19 prognosis. Normally under 0.5 µg/mL, its levels increase in severe infections. Admission D-dimer has shown potential in predicting disease severity [19]. COVID-19 mortality rates range from 3% to 25%, depending on the study [20]. The present study assessed outcomes such as oxygen therapy, ICU admission, and need for ventilation.

Methods

This retrospective, cross-sectional, record based and single-centre study was conducted on all 484 COVID 19 positive patients admitted to a tertiary care Hospital in Mumbai over period of one year during second wave of COVID 19. Approval from the Institutional Ethics Committee and Review Board was taken. Patients were recruited according to the WHO directions with either positive Rapid antigen test (RAT) or RT-PCR or CBNAAT for SARS-COV-2 and a known IL-6 and D- Dimmer measurement at admission. Patients who were not admitted or managed on OPD basis, and patients less than 12 years of age were excluded from the study. On admission, study variables related to identification History, History of present illness and variables related to prognosis like Presence of comorbidity e.g. Diabetes mellitus, hypertension, Renal disease, cancers etc. were gathered. General and systemic examination findings were included routine blood investigations and pro-inflammatory factors like IL-6 value & D-Dimer levels were analysed following the hospital standardised protocols. Radiological examinations and other imaging modalities if required, were also recorded. Various outcome variable including hospital stay days, oxygen requirement, admission to the ICU, and mortality were documented. Statistical analyses were done using OpenEpi version 2.3 Dated 2009/20/5. Data compilation was done using Microsoft Excel 2010 and analysis was done using SPSS version 21. Descriptive statistic (Percentage, mean, standard deviation) was used to summarize baseline characteristics of the study participant. An association between two categorical variables was analyzed by using the Chi - square test. For studying relation between continuous variable Bivariate correlation was used. The results were interpreted and compared with various studies done previously.

Results

This study is a hospital-based retrospective, cross-sectional, record based and single-centre study encompassing 484 COVID 19 positive patients admitted to a tertiary care Hospital of Mumbai city. The study evaluated the clinical profile, particularly IL- 6 and D-Dimer levels and its association with clinical outcome. Majority of the patients (72.31%) were male and 27.69% were female. Most common age group involved was 41-60 years of i.e. 41.5% followed by 28.9% in age group of 21- 40 years and 22.3% in 61- 80 years group and least among > 80 years (4.5%). The leading symptom was fever (79.5%) followed by Cough (50.9%), Dyspnoea (31.6%), Chest Distress (16.9%), Fatigue (14.1%), Diarrhoea (12.3%), Nausea and Vomiting (4.1%) and Sore Throat (2.3%). Among different comorbidities, diabetes mellitus (50.3%) was the most prevalent, followed by hypertension (25.9%), ischemic heart disease (8.2%) and COPD (5.4%). Chronic renal failure (1.4%), cerebrovascular accident (2.0%) and Tuberculosis (4.1%) were the other comorbidities reported. Out of 484 patients, 277 (57.23%) patients maintained saturation above 95% on room air, 89 (18.39%) patients required nasal prongs (Oxygen up to 4 litres), 57 (11.78%) patients required Oxygen more than 4lit/min i.e. needed face mask & Non-rebreather mask, 30 (6.30%) patients went on Non-invasive ventilation and 28 (5.79%) patients required invasive mechanical ventilation either on admission or at some point during their hospital stay. 75.21% patients had normal D- dimer level while remaining 24.79% had raised D- dimer level i.e. > 5 mcg/dl. 343 (70.87%) patients had IL- 6 level < 30pg/dl and 141(29.13%) patients showed raised IL-6 level i.e. > 30pg/dl. It was observed that 356 (73.55%) patients were discharged while 128 (26.45%) patients died in our study. 76.29 % males were discharged and 23.71% males died, 66.42% females were discharged, and 33.58 % females died. The proportion of death among female is more than male which was found statistically significant. **(Chi-square value= 4.357, p=0.018 (< 0.05)**. There were 22 patients in above 80 age group out of which 45.45% were discharged and 54.55% patients died, 108 patients in 61 to 80 years age group out of which 53.70% were discharged and 46.30% patients died, 201 patients in age group of 41 to 60 years among them 73.63% discharged and 26.37 died and 140 patients in 21 to 40 years age group out of which 92.14% were discharged and 7.86% died. There was significantly higher incidence of death in as age increases which found statistically significant. **(Chi-square value= 56.49, p=0.00001 (< 0.05)**. Proportion of deaths was higher among those who were needed oxygen support which found statistically significant **(Chi-square value= 295.4, p=0.00001 (< 0.05)**. Patients without any comorbidity had a discharge rate of 81.31% and death rate of 18.69% as compared to those with comorbidities, wherein 55.78% were discharged and 44.22% died. There was significantly higher incidence of death in patients with comorbidities **(chi-square = 32.98, p < 0.0001)**. IL-6 level was found to be one of the most important determinants of patient outcome in COVID patients. This study found that death rate among those with raised IL-6 level (> 30pg/dl) was higher (86.05%) compared to those with normal IL-6 level (< 30pg/dl) i.e. 10.94% deaths **(Chi- square =226.0, p < 0.000001)**. The study also found that death rate among those with raised D-Dimer level (> 5 mcg/dl) was higher (93.33%) compared to those with normal D-Dimer level (< 5 mcg/dl) i.e. 4.40% deaths **(chi- square = 362.4, p < 0.00001)**.

Table 1: Distribution of Patients According to Age

Sex	Frequency (N)	Percentage (%)
Male	350	72.31
Female	134	27.69
Total	484	100

Table 2: Age Wise Distribution of Covid 19 Positive Patients

Age	Frequency (N)	Percentage (%)
Upto 20 Yrs	13	2.7
21-40 Yrs	140	28.9
41-60 Yrs	201	41.5
61- 80 Yrs	108	22.3
> 80 Yrs	22	4.5
Total	484	100.0

Table 3: Distribution of Patients According to Symptoms

Symptoms	Frequency (N)	Percentage (%)
Fever	385	79.5
Sore Throat	11	2.3
Cough	246	50.9
Dyspnea	153	31.6
Diarrhea	60	12.3
Fatigue	68	14.1
Nausea/Vomiting	20	4.1
Chest Distress	82	16.9

Table 4: Distribution of Covid Patients According to Different Comorbidities

Comorbidities	Frequency (N)	Percentage (%)
Hypertension	38	25.9
Bronchial Asthama	3	2.0
Diabetes Mellitus	74	50.3
COPD	8	5.4
CKD	2	1.4
CVA	3	2.0
IHD	12	8.2
TB	6	4.1
Hypothyroidism	1	0.7

Table 5: Distribution of Patients According to O_2 Requirement

Modes of Oxygen Requirement	Frequency (N)	Percentage (%)
Nasal Prongs	89	18.39
NRBM	57	11.39
NIV	30	6.30
Ventilator	28	5.79
Total	207	100.00

Table 6: Distribution of Patients According to D- Dimer Level

D- Dimer	Frequency (N)	Percentage (%)
<5 mcg/dl	364	75.21
> 5 mcg/dl	120	24.79
Total	484	100.00

Table 7: Distribution of Patients According to Il-6 Level

Il-6 Level	Frequency (N)	Percentage (%)
< 30 pg/dl	343	70.87
>30 pg/dl	141	29.13
Total	484	100.00

Table 8: Distribution of Patients According to Outcome

Patient Outcome	Frequency (N)	Percentage (%)
Discharge	356	73.55
Death	128	26.45
Total	484	100.00

Table 9: Comparison of Sex with Patient Outcome

	Discharge		Death		Total
Sex	N	%	N	%	Total
Male	267	76.29	83	23.71	350
Female	89	66.42	45	33.58	134
Total	356	73.55	128	26.45	484

Chi-square value= 4.357, p=0.018 (< 0.05)

Table 10: Comparison of Age Wise Distribution and Patient Outcome

Age	Discharge		Death		Total
	N	%	N	%	
Upto 20 Yrs	11	84.62	2	15.38	13
21-40 Yrs	129	92.14	11	7.86	140
41-60 Yrs	148	73.63	53	26.37	201
61- 80 Yrs	58	53.70	50	46.30	108
> 80 Yrs	10	45.45	12	54.55	22
Total	356	73.55	128	26.45	484

Chi-square value= 56.49, p=0.00001 (< 0.05)

Table 11: Comparison of Mode of O_2 Intervention and Outcome.

Mode of Oxygenation		Discharge		Death		Total
	N		%	N	%	
No Oxygen		276	99.64	1	0.36	277
Nasal O2		55	61.80	34	38.20	89
Face Mask & NRBM		21	36.84	36	63.16	57
Ventilator& NIV		4	6.56	57	93.44	61
Total		356	73.55	128	26.45	484

Chi-square value= 295.4, p=0.00001 (< 0.05)

Table 12: Comparison of Presence of Comorbidities and Outcome.

Presence of Comorbidities		Discharge			DE	ATH	Total
	N		%	N		%	
With Comorbidities		82	55.78		65	44.22	147
No Comorbidities		274	81.31		63	18.69	337
Total		356	73.55		128	26.45	484

Chi-square value= 32.98, p=0.00001 (< 0.05)

Table 13: Comparison of Il-6 and Outcome.

IL-6 Level		Discharge			Death		Total
	N		%	N		%	
≤ 30 pg/dl		342	89.06		42	10.94	384
> 30pg/dl		14	14.00		86	86.00	100
TOTAL		356	73.55		128	26.45	484

Chi-square value= 226, p < 0.00001 (< 0.05)

Table 14: Comparison of D-Dimer Level and Patient Outcome.

D- Dimer Level		Discharge			Death		Total
	N		%	N		%	
< 5 mcg/dl		**348**	**95.60**		**16**	**4.40**	**364**
> 5 mcg/dl		**8**	**6.67**		**112**	**93.33**	**120**
TOTAL		**356**	**73.55**		**128**	**26.45**	**484**

Chi-square value= 226, p < 0.00001 (< 0.05)

Discussion

This study is a hospital-based, retrospective, cross-sectional, record-based, and single-centre study encompassing 484 COVID-19 positive patients admitted to a tertiary care hospital in Mumbai city. The objectives were to study the clinical profile, IL-6 and D-Dimer levels, and their association with clinical outcomes.

In our study, it was observed that the majority of the patients (72.31%) were male, while 27.69% were female. A study by Maria Martinez-Urbistondo *et al*. found that, out of a study population of 165, 66% were men and 33% were women [21]. A study by Dhruv Talwar *et al*., conducted at Acharya Vinoba Bhave Rural Hospital, Sawangi, Wardha, reported 74% males and 26% females, which is similar to the present study [22]. Poudel A. *et al*. reported that, among 182 enrolled candidates, 113 (62.1%) were male and 69 (37.9%) were female [19].

In the present study, the majority of the patients (41.5%) were in the age group of 41–60 years, followed by 28.9% in the 21-40 years group, and 22.3% in the 61-80 years group. A total of 4.5% were above 80 years of age, with the least number being under 20

years. The mean age of the study population was 49.82 years with a standard deviation of ±17.14. Similar findings were observed in a study by Soni M. *et al*., where the median age was 61 years, ranging from 21 to 89 years. Of the 483 patients, 59.6% (288) were adults (21–64 years), and 40.3% (195) were elderly (older than 65 years)[23].

In the present study, it was observed that the most common symptom among COVID-19 patients was fever (79.5%), followed by cough (50.9%), dyspnoea (31.6%), chest distress (16.9%), fatigue (14.1%), diarrhoea (12.3%), nausea and vomiting (4.1%), and sore throat (2.3%). In a retrospective case series study by Li P. *et al*., the main presenting symptoms included fever (78.9%), cough (49%), dyspnoea (31.9%), sputum production (18.1%), chest distress (16.2%), fatigue (15.2%), anorexia (15.2%), diarrhoea (13.2%), and myalgia (8.8%) [24].

Out of 484 patients, 147 had comorbidities. Among these, the most prevalent were diabetes mellitus (50.3%), hypertension (25.9%), ischemic heart disease (8.2%), and COPD (5.4%). Chronic renal failure, cerebrovascular accident (CVA), and tuberculosis were reported in 2 (1.4%), 3 (2.0%), and 6 (4.1%) patients respectively. A study by A. Avila-Nava *et al*. found that the most common comorbidities were diabetes and hypertension (34%) and overweight or obesity (42.10%). Additionally, 8% of individuals were living with HIV and under antiretroviral treatment [25]. Li P. *et al*. reported that 140 (68.8%) had one or more comorbidities: hypertension (36.3%), diabetes (17.6%), cardiovascular disease (14.5%), and COPD (10.3%) [24]. Maria Martinez-Urbistondo *et al*. reported 44% with arterial hypertension, 53% with dyslipidaemia, and 33% with diabetes [21].

In the present study, out of 484 patients, 277 (57.23%) maintained oxygen saturation above 95% on room air; 89 (18.39%) required nasal prongs (O2 up to 4 litres); 57 (11.78%) required O2 more than 4 litres/min, i.e., face mask or NRBM; 30 (6.30%) went on NIV; and 28 (5.79%) required mechanical ventilation either on admission or during the hospital stay. Similar findings were seen in a study by Jain SK *et al*., which found oxygen saturation was 71.82±17.15% and respiratory rate was 30.20±6.58 per minute [26]. In a study by Yao *et al*., 67.7% of patients received oxygen therapy, including nasal cannula/face mask (52.0%), non-invasive mechanical ventilation (10.5%), invasive mechanical ventilation (5.2%), and extracorporeal membrane oxygenation in one patient[27].

In the present study, 356 (73.55%) patients were discharged, while 128 (26.45%) patients died. Similar results were found in a study by de Souza R. *et al*., where 77.36% of admitted 689 patients were discharged alive and 22.64% died [28]. In our study, of the 277 patients who maintained saturation above 95% on room air, a higher proportion were discharged. Among those on nasal oxygen, 61.80% were discharged and 38.2% died; among those on face mask or NRBM, 36.84% were discharged and 63.16% died. Patients on NIV and mechanical ventilation had a 93.44% death rate. This association between oxygen mode and death rate was statistically significant (Chi-square = 295.4, $p < 0.00001$). W. Guan *et al*. found a primary composite end-point in 67 patients (6.1%), including 5.0% admitted to ICU, 2.3% who underwent invasive mechanical ventilation, and 1.4% who died-similar to our findings [29]. De Souza R. *et al*. also reported that 11.61% required oxygen support and 2.8% required ICU admissions [28].

In the present study, patients without comorbidities had a discharge rate of 81.31% and a death rate of 18.69%. In contrast, those with comorbidities had a discharge rate of 55.78% and a death rate of 44.22%. This difference was statistically significant (Chi-square = 32.98, $p < 0.0001$). De Souza R. *et al*. also reported that comorbidities were associated with an increased risk of death [28]. El-Shabrawy *et al*. found that comorbidities were significantly higher in non-survivors (87.5%) than survivors (31.5%) ($P = 0.001$) [30]. M. Soni *et al*. reported that 89% of fatal cases had underlying disease, and 70% of these had diabetes. The association between comorbidities and survival was statistically significant ($P < 0.01$, HR = 25.01) [23].

IL-6 level is an important determinant of patient outcomes in COVID-19. In our study, patients with IL-6 > 30 pg/dl had a death rate of 86.05%, compared to 10.94% among those with IL-6 < 30 pg/dl (Chi-square = 226.0, $p < 0.000001$). A similar study by Azalia Avila-Nava *et al*. found higher serum IL-6 levels in non-survivors (median = 45.60 pg/mL) compared to survivors (median = 10 pg/mL). The optimal cutoff was 30.95 pg/mL (sensitivity = 78.6%, specificity = 79.2%, Youden Index = 0.57) [25]. In a study by Dhruv Talwar *et al*., the mean IL-6 in discharged patients was 965.47 pg/mL (±2055.24), and in expired patients was 997.57 pg/mL (±1240.51) [22]. Maria Martinez-Urbistondo *et al*. also showed that IL-6 levels were significantly associated with in-hospital mortality [21].

D-Dimer level on admission is another crucial determinant of outcomes. In our study, the death rate among those with D-Dimer > 5 mcg/dl was 93.33%, compared to 4.40% among those with D-Dimer < 5 mcg/dl (Chi-square = 362.4, $p < 0.00001$). A similar study by Mamta Soni *et al*. showed that D-Dimer > 5.0 mcg/dl was a significant predictor of death. High D-Dimer levels (> 50 mcg/dl) were found in 96% (72/75) of fatal cases; 74.67% (56/75) had D-Dimer > 5.0 mcg/dl. Ayusha Poudel *et al*. found 1.5 µg/ml to be the optimal D-Dimer cutoff for mortality prediction. The mean admission D-Dimer was 1.067 µg/ml (±1.705) in survivors and 3.208 µg/ml (±2.613) in those who died [23]. Yumeng Yao *et al*. found D-Dimer > 2.0 mg/L at admission was significantly associated with increased mortality [27].

Declarations

Ethics Approval

The study was approved by the Institutional Ethics Committee of HBT MEDICAL COLLEGE & Dr RN Cooper Hospital, Mumbai, Maharashtra.

Availability of supporting data

The datasets generated and/or analysed during the current study are available from the corresponding author on reasonable request.

Conflicts of interest

None

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All authors have declared that no financial support was received from any organization for the submitted work.

Financial relationships

All authors have declared that they have no financial relationships at present or within the previous three years 9 of 10 with any organizations that might have an interest in the submitted work.

Author's contributions

Prakash Ram Relwani, Ashvinkumar Hake and Neelam N. Redkar conceptualised the study and were the principal investigators.

Omkar E. Paradkar, and Karan Desai assisted with data interpretation and literature review. Diksha Samsukha assisted with manuscript writing. Alhad Mulkalwar assisted in the final review of the manuscript. All authors read and approved the final manuscript.

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