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Predictors of mortality in COVID-19 disease

Srikanth AK[1], Vijayalakshmi KP[2], Naveen S Kulkarni[3], Bhanuprathap Hoskeri[4], Hithashree C Shriyan[5], Nalla Yeshwanth Kirankumar[6]

[1,2]Assistant Professor, [3]Associate Professor, [4,5,6]Postgraduate Resident, Department of General Medicine, Shri Dharmasthala Manjunatheshwara College of Medical Sciences and Hospital, Shri Dharmasthala Manjunatheshwara University, Dharwad, Karnataka, India

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ABSTRACT

Background: COVID-19, an acute viral respiratory illness, was first noted in 2019, soon turned into pandemic with considerable mortality. With the objective of studying effect of comorbidities on COVID-19 disease severity and to identify laboratory markers associated with severe COVID-19 disease, we did a retrospective observational study in a tertiary care centre. **Aims and Objectives:** The objectives of this study were as follows: 1. To study effect of comorbidity on COVID-19 disease severity and 2. to identify laboratory markers associated with severe COVID-19 infection and mortality. **Materials and Methods:** This is an retrospective observational study conducted at SDMCMS&H, Dharwad from July 2020 to September 2020. A total of 402 cases who fall in the age group of 18 years and above were collected from medical record department. Statistical analysis used: The data were recorded in the Microsoft Excel sheet and analysis is done using Chi-square analysis and Cox linear regression method. **Results:** There were 402 patients whose data were collected. Out of 402 patients, 64 patients (15.92%) were in the age group of 18–39 years, 183 patients (45.52%) seen were in the age group of 40–60 years, 155 patients (38.56%) above 60 years, and consisting 291 male patients (72.39%) and 111 female patients (27.9%). Most common comorbidities seen were diabetes mellitus in 194 patients (48.26%) and hypertension in 182 patients (45.27%), followed by chronic kidney disease in 32 patients (7.96%) and ischemic heart disease in 24 patients (5.97%). Out 402 patients, 141 patients (35.07%) were on supplemental oxygen, which included 68 patients (48.23%) on low flow oxygen by face mask, seven patients (4.96%) were on non-rebreathing mask, 3 (2.13%) patients required NIV, and 63 patients (44.68%) required intubation and mechanical ventilation. It was found that uncontrolled diabetes rather than just presence of diabetes had significant impact on mortality with P = −0.0001 (95% CI OR 1.5–4.38). Patients with increased laboratory markers of inflammation such as Ferritin (95% CI OR 1.84–6.81) and LDH (95% CI OR 1.86–31.26) had strong association with mortality. The presence of thrombocytopenia showed significant association with mortality (95% CI OR 1.03–3.63). **Conclusion:** The presence of preceding uncontrolled hyperglycemia has significant effect on mortality. A state of hyperinflammation is directly associated with poor outcome.

Key words: Cytokine storm; Diabetes mellitus; Hyperferritinemia; Severe COVID-19; Thrombocytopenia

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INTRODUCTION

It is well known that COVID-19 pandemic has been growing, and hence, identifying patients who need prompt inpatient management are crucial to prevent mortality. Although clinical profiles such as presence of comorbidities and low peripheral oxygen saturation (SpO_2) have been in use to triage patients, laboratory parameters might help sub-triaging among such patients, since the prevalence of comorbidities such as diabetes, hypertension, ischemic heart disease (IHD), and chronic kidney disease (CKD) is high and it is often too late to defer until SpO_2 drops. Our study was done to identify parameters that can predict mortality in COVID-19.

Address for Correspondence:
Dr. Vijayalakshmi KP, Assistant Professor, Department of General Medicine, Shri Dharmasthala Manjunatheshwara College of Medical Sciences and Hospital, Shri Dharmasthala Manjunatheshwara University, Dharwad, Karnataka, India. **Mobile:** 6360938654.
E-mail: kplakshmi714@gmail.com

Aims and objectives

The objectives of this study were as follows:

1. To study effect of comorbidity on COVID-19 disease severity
2. To identify laboratory markers associated with severe COVID-19 infection and mortality

Inclusion criteria

All patients admitted during study period with positive RTPCR/RAT report for COVID-19 were included in the study.

Exclusion criteria

The following criteria were excluded in the study:

Age <18 years.

MATERIALS AND METHODS

Our study was retrospective observational study. Data were collected from medical records of patients admitted to our hospital from July 2020 to September 2020 in COVID wards and COVID ICU after the Institutional Ethical Clearance. This time duration was chosen in view of pandemic peak in our region. Data were collected regarding clinical profile of patients, presence of comorbidities such as diabetes mellitus, hypertension, IHD, CKD, malignancy, HIV, and requirement of oxygen status/ventilation, laboratory parameters including complete blood count, renal and liver function tests, HbA1C, and inflammatory markers such as CRP, LDH, and Ferritin. IL-6 reports were not available in our patient records. Chi-square and simple cox regression model were used to analyze association between various parameters and mortality.

Ethical committee

Permissions – taken from the Institutional Ethics Committee and medical records department (Ref: SDMIEC/2021/13, date: 15/07/2021).

RESULTS

There were 402 patients whose data were collected. Out of 402 patients, 64 patients (15.92%) were in the age group of 18–39 years, 183 patients (45.52%) seen were in the age group of 40–60 years, 155 patients (38.56%) above 60 years, and consisting 291 male patients (72.39%) and 111 female patients (27.9%). Prevalence of comorbidities is shown in Table 1. Most common comorbidities seen were diabetes mellitus in 194 patients (48.26%) and hypertension in 182 patients (45.27%), followed by CKD in 32 patients (7.96%) and IHD in 24 patients (5.97%).

Severity distribution of COVID patients-by oxygen requirements is shown in Table 2. Out 402 patients, 141 patients (35.07%) were on supplemental oxygen, which included 68 patients (48.23%) on low flow oxygen by face mask, seven patients (4.96%) were on non-rebreathing mask, 3 (2.13%) patients required NIV, and 63 patients (44.68%) required intubation and mechanical ventilation. Laboratory parameters are shown in Table 3. Statistical analysis is shown in Table 4 and Table 5. It was found that uncontrolled

Table 1: Prevalence of comorbidities

Comorbidities	Present (n)	Prevalence (%)
Diabetic mellitus	194	48.26
Hypertension	182	45.27
Chronic kidney disease	32	7.96
Interstitial lung disease	1	0.25
Ischemic heart disease	24	5.97
Malignancy	3	0.75

Table 2: Severity distribution of COVID patients-by oxygen requirements

Oxygen requirements	Present (n)	Prevalence (%)
Without oxygen	261	64.93
With oxygen	141	35.07
Out of 141		
By mask	68	48.23
NRBM	7	4.96
NIV	3	2.13
Intubation	63	44.68

Table 3: Distribution of COVID patients by status of different laboratory parameters

	Number of COVID patients (n)	% of COVID patients
DM-HbA1C (%)		
<6.5	208	51.74
6.5–9.9	146	36.31
≥10	48	13.45
Sodium		
≤135	139	38.94
>135	218	61.06
TLC		
≤4000	41	11.48
4001–10999	244	68.35
≥11000	72	20.17
Platelet (in lakhs)		
<1.5 lakhs	47	13.24
≥1.5 lakhs	308	86.76
Ferritin		
≤300	179	50.14
>300	178	49.86
C-reactive protein		
<6	87	26.13
6–49	117	35.14
50–100	46	13.81
>100	83	24.92
LDH		
<230	88	26.04
≥230	250	73.96
NLR		
<2	68	19.05
≥2	289	80.95

Table 4: Association between mortality and factors – *P<0.05

Factors	Improved	%	Death	%	Total	Chi-square	P-value
DM (HbA1c %)							
No	177	85.10	31	14.90	208		
Yes	163	84.02	31	15.98	194	11.2359	0.7650
Control of DM							
Non diabetic (<6.5)	177	85.10	31	14.90	208		
Controlled DM (6.5–9.9)	131	95.63	6	4.37	137		
Uncontrolled DM (≥10)	32	56.15	25	43.85	57	41.1740	0.0001*
HTN							
No	188	85.45	32	14.55	220		
Yes	152	83.52	30	16.48	182	3.4843	0.5920
Ischemic heart disease							
No	324	85.71	54	14.29	378		
Yes	16	66.67	8	33.33	24	6.2770	0.0120*
Sodium							
≤135	123	78.85	33	21.15	156	6.4190	0.0110*
>135	217	88.21	29	11.79	246		
TLC							
≤4000	37	86.05	6	13.95	43		
4001–10999	242	87.68	34	12.32	276		
≥11000	61	73.49	22	26.51	83	9.9260	0.0070*
Platelet (in lakhs)							
<1.5 lakhs	39	76.47	12	23.53	51	2.8770	0.0900
≥1.5 lakhs	299	85.67	50	14.33	349		
Ferritin							
≤300	185	94.39	11	5.61	196	28.2220	0.0001*
>300	155	75.24	51	24.76	206		
C-reactive protein							
<6	105	32.01	8	67.99	113		
>6	223	80.50	54	19.50	277	9.25	0.002*
LDH							
<230	89	97.80	2	2.20	91		
≥230	229	80.07	57	19.93	286	16.4440	0.0001*
NLR							
<2	68	100.00	0	0.00	68		
≥2	250	86.51	39	13.49	289	10.3020	0.0010*

diabetes rather than just presence of diabetes had significant impact on mortality with P=−0.0001 (95% CI OR 1.5–4.38). Patients with increased laboratory markers of inflammation such as Ferritin (95% CI OR 1.84–6.81) and LDH (95% CI OR 1.86–31.26) had strong association with mortality. The presence of thrombocytopenia showed significant association with mortality (95% CI OR 1.03–3.63).

DISCUSSION

Diabetes and COVID-19

Since SARS-COV-2 causes intense inflammatory state, it is difficult to point whether hyperglycemia during admission is the cause or consequence of the disease. Besides steroids being included as standard of care in patients requiring oxygen/ventilation, cause effect relationship is further entangled.

We observed that patients who had preceding uncontrolled diabetes mellitus as reflected by HbA1c >10 had higher mortality compared to non-diabetic and diabetic with adequate control of sugars before the infection. Furthermore, when analyzed for diabetic patient versus non-diabetic this association was not strong, implying control of hyperglycemia preceding the infection might mitigate the risk of severe COVID in diabetic patient.

An analysis of national diabetes and mortality data from the United Kingdom[1] before and during the pandemic (over 10,000 COVID-19-related deaths in people with diabetes [predominantly type 2]) showed an association between preceding hyperglycemia and mortality.

Studies conducted in Scotland[2] and Swedish population[3] found association of uncontrolled diabetes with mortality in COVID-19.

Other comorbidities

In our study, hypertension, IHD, and CKD did not show any significant association with mortality.

Hematological parameters

Thrombocytopenia

We observed that patients who had thrombocytopenia had higher mortality with statistical P value of 0.0410 (95% CI OR 1.03–3.63).

Table 5: Simple Cox regression model of mortality by various parameters *P<0.05

Factors	Unadjusted OR	95% CI for OR		P-value
		Lower	Upper	
DM				
No	Reference			
Yes	0.85	0.51	1.40	0.5210
HTN				
No	Reference			
Yes	0.89	0.54	1.47	0.6510
Ischemic heart disease				
No	Reference			
Yes	1.13	0.52	2.46	0.7630
HbA1C				
<10	Reference			
≥10	2.61	1.55	4.38	0.0001*
Sodium				
>135	0.64	0.39	1.06	0.0820
≤135		Reference		
TLC				
≤4000	Reference			
4001–10999	1.10	0.46	2.63	0.8310
≥11000	1.88	0.76	4.65	0.1730
Platelet (in lakhs)				
<1.5 lakhs	1.93	1.03	3.63	0.0410*
≥1.5 lakhs	Reference			
Ferritin				
≤300	Reference			
>300	3.54	1.84	6.81	0.0001*
C-reactive protein				
<6	Reference			
>6	1.82	0.857	3.85	0.119
LDH				
<230	Reference			
≥230	7.63	1.86	31.26	0.0050*
D Dimer				
≤500	Reference			
>500	0.66	0.30	1.45	0.2980
NLR				
<2	Reference			
≥2	26.45	0.39	1794.88	0.1280

The presence of thrombocytopenia as a prognostic marker of inflammation/sepsis was widely known. Possible mechanisms might also be similar including but not limited to aggregation of platelets at the site of endothelial injury as in any case of pneumonia, hemophagocytic lymphohistiocytosis during cytokine storm, suppression of megakaryopoiesis, and increased peripheral destruction due to formation of immune complexes.

A meta-analysis done by Lippi et al.,[4] showed that low platelet count is associated with increased risk of severe disease and mortality in patients with COVID-19 and, thus, should serve as clinical indicator of worsening illness during hospitalization

A meta-analysis done by Pranata et al.,[5] showed that thrombocytopenia was associated with poor prognosis in patients with COVID-19.

Total and differential leukocyte count-concept of increased NLR

We did not find any statistically significant association of leukocytosis or leukopenia, high NLR ratio with mortality.

Neutrophils can be triggered by virus-related inflammatory factors, such as interleukin-6 and interleukin-8, tumor necrosis factor-alpha and granulocyte colony stimulating factor, and interferon-gamma factors, produced by lymphocyte and endothelial cells. On the other hand, human immune response triggered by viral infection mainly relies on lymphocyte, whereas systemic inflammation significantly depresses cellular immunity, which significantly decreases CD4+ T lymphocytes and increases CD8+ suppressor T lymphocyte. Thus, virus-triggered inflammation increased NLR.

Other studies done so far in COVID-19 have found positive association of high NLR with progression and mortality.[6]

Parameters of hyperinflammation

Hyperferritinemia

We observed that patients who had high ferritin had higher mortality.

It is well known that ferritin is associated with immunosuppressive and proinflammatory state and is regarded as marker of hyperinflammation.

In our study, we found that hyperferritinemia was associated with mortality which was statistically significant.

An Italian study conducted by Carubbi et al.,[7] demonstrated that high ferritin is associated with severity of lung involvement but not the disease prognosis.

Study done by Bozkurt et al.,[8] showed that ferritin is associated with severe COVID and mortality.

A cross-sectional study conducted by Ahmed et al.,[9] concluded that ferritin level on admission is associated with mortality, though not a reliable marker of severity.

C-reactive protein (CRP)

We did not find statistical significant association of mortality with CRP.

Many studies done; worldwide shows that CRP can be marker of disease progression and severe pneumonia in COVID-19.

Hypercoagulability

We did not find any statistically significant association of D dimer with mortality. A limitation in our study was only

few patients had their d dimer levels checked as per the treating physician discretion.

There have been few published literatures on thrombotic events in COVID-19. Some studies have highlighted association between COVID-19 pneumonia and formation of microthrombi in pulmonary microvasculature.

However, in our statistical analysis, it was not found to be significant.

Limitations of the study

1. IL-6 reports were not available.
2. Serial monitoring of CRP reports was not available for patients who deteriorated or improved

CONCLUSION

The presence of preceding uncontrolled hyperglycemia has significant effect on mortality. A state of hyperinflammation is directly associated with poor outcome.

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Authors' Contributions:
SAK – contributed by formulating the concept and design of the study, acquisition of data, analysis, and interpretation of the results. He was also actively involved in drafting the article, revising it critically and final approval of the manuscript; **VKP –** contributed in collection of data, analysis, and interpretation of results and drafting the article; **NSK –** was involved in the planning of study design, acquisition of data, critically reviewing the article and in final approval; **BH, HCS, and NYK –** were actively involved in data acquisition, analysis of results, statistical analysis, interpretation of results, and critical review of the article from time to time

Work attributed to:
Shri Dharmasthala Manjunatheshwara College of Medical Sciences and Hospital, Shri Dharmasthala Manjunatheshwara University, Dharwad - 580 009, Karnataka, India

Orcid ID:
Dr. Srikanth AK - https://orcid.org/0000-0002-7793-5643
Dr. Vijayalakshmi KP - https://orcid.org/0000-0001-5550-0959
Dr. Naveen S Kulkarni - https://orcid.org/0000-0002-1219-299X
Dr. Bhanuprathap Hoskeri - https://orcid.org/0000-0002-6711-3283
Dr. Hithashree C Shriyan - https://orcid.org/0000-0003-4653-9311
Dr. Nalla Yeshwanth Kirankumar - https://orcid.org/0000-0001-8094-0577

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