

# A Retrospective Observational Study of Hypoxic COVID-19 Patients Treated with Immunomodulatory Drugs in a Tertiary Care Hospital

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## ABSTRACT

**Objectives:** To describe the demographics and evaluate the clinical outcomes of hypoxic coronavirus disease-2019 (COVID-19) patients treated with different immunomodulatory (IM) drugs in a resource-limited setting.

**Materials and methods:** We conducted a retrospective cohort study of these patients admitted to our hospital between March 22 and May 31, 2020. Data were abstracted from multiple electronic data sources or patient charts to provide information on patient characteristics, clinical, laboratory variables, and outcomes.

**Results:** A total of 134 patients met the inclusion criteria and were followed up till June 7, 2020. The median age of the patients was 55.6 years (range 20–89 years) and 68% were men. At least one comorbidity was seen in 72% of the patients with diabetes (44%) and hypertension (46%) being the most common. At triage, fever (82%), shortness of breath (77%), and cough (61%) were the most common presenting symptoms. A PaO<sub>2</sub>/FiO<sub>2</sub> ratio less than 300 was seen in 60%, and 4.5% required invasive mechanical ventilation within 72 hours of hospital admission. Five immunomodulatory agents (hydroxychloroquine, methylprednisolone, colchicine, etoricoxib, and tocilizumab) were administered in different combinations. Overall, in-hospital mortality was 26.9%, and 32% required mechanical ventilation. Around 69% of patients were discharged home. Five variables (SpO<sub>2</sub>, PaO<sub>2</sub>/FiO<sub>2</sub> ratio, leukocytosis, lymphopenia, and creatinine) on admission were found to be significant in the patients who died.

**Conclusion:** Our study provides the characteristics and outcomes of hypoxic COVID-19 patients treated with IM drugs in varied combination. Five independent variables were strong predictors of mortality.

**Keywords:** Acute respiratory distress syndrome, Coronavirus disease-2019, Immunomodulatory drugs, Resource-limited settings.

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## INTRODUCTION

India reported the first case of coronavirus disease-2019 (COVID-19) on January 30, 2020.<sup>1</sup> The World Health Organization (WHO) declared COVID-19 as pandemic on March 11, 2020, and our hospital admitted the first COVID patient on March 22. Though the exact pathogenesis of severe acute respiratory syndrome-coronavirus-2 (SARS CoV-2) is unknown, various hypotheses have proposed cytokine storm or hyperinflammatory syndrome as probable causes for rapid worsening of the disease. To date, there is no evidence that any potential therapy improves outcomes in patients with COVID-19<sup>2–4</sup> and various antiviral and immunomodulatory (IM) drugs have been repurposed for the treatment of COVID-19.

Currently, there is no published data about baseline characteristics, clinical features, and outcomes from India. Considering the impact the disease has on the public health especially in a resource-limited country like ours, we conducted a retrospective cohort study of the demographics and outcomes of hypoxic COVID-19 patients admitted to our hospital who were treated with various IM agents.

The pharmacology and rationale for use of these IM agents in COVID-19 are depicted in Table 1.

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**Table 1:** Drug pharmacology<sup>5,6</sup>

Drug class	Clinical experience	Mechanism	Rationale for use in COVID-19	Dosage	Adverse effects
Colchicine-alkaloid Antitumor agent	GRECCO-19 trial <sup>17</sup>	Exerts anti-inflammatory and IM effects by inhibition of tubulin polymerization causing disruption of cytoskeletal functions and inhibition of nucleotide oligomerization domain (NOD)-like receptors protein 3 (NLRP3) inflammatory assembly	Might diminish or ameliorate the COVID-19 inflammatory storm associated with severe forms of the disease by suppressing proinflammatory cytokines and chemokines 2	0.5 mg/day for 1 week	Common: Diarrhea, vomiting Serious: Myelosuppression
Methylprednisolone Synthetic corticosteroid	Fadel et al. <sup>15</sup>	Inhibit the synthesis of TNF- $\alpha$ , IL-6, monocyte migration, and the secretion of matrix metalloproteinase-9 Binds to and activates specific nuclear receptors, resulting in altered gene expression and inhibition of proinflammatory cytokine production	With potent anti-inflammatory and antifibrotic properties, low doses of corticosteroids may prevent an extended cytokine response and may accelerate resolution of pulmonary and systemic inflammation in pneumonia	1 mg/kg in two divided doses for 5 days	Cardiovascular: Congestive heart failure Endocrine metabolic: Cushing's syndrome, hyperglycemia, primary adrenocortical insufficiency Hepatic: hepatotoxicity Musculoskeletal: Osteoporosis QT interval prolongation
Hydroxychloroquine	Borba et al. <sup>24</sup>	Impairs the terminal glycosylation of the angiotensin-converting enzyme 2 (ACE2) receptor, which is the binding site for the envelope spike glycoprotein and has been shown to inhibit endolysosome function	As inhibitors of heme polymerase, they are also believed to have additional antiviral activity via alkalization of the phagolysosome, which inhibits the pH-dependent steps of viral replication	400 mg Day 1	
Alkylated 4-aminoquinolines Antimalarial	Chorin et al. <sup>25</sup>			200 mg $\times$ 5 days	Cardiomyopathy
Tocilizumab Humanized monoclonal antibody directed against IL-6 receptor	Klopfenstein et al. <sup>14</sup> Guaraldi et al. <sup>15</sup>	Humanized monoclonal antibody targeting both forms of the IL-6 receptor (membrane-bound and soluble)	Blocking the IL-6 pathway might reduce the vigorous inflammatory response reducing the cytokine storm	8 mg/kg (up to a maximum of 800 mg per dose), with an interval of 12 hours	Hypoglycemia Gastrointestinal: Gastrointestinal perforation, pancreatitis Hematologic: Decreased platelet count, neutropenia Hepatic: Hepatotoxicity Immunologic: Anaphylaxis, hypersensitivity reaction, opportunistic infection, tuberculosis
Etoricoxib Selective COX-2 inhibitor	Sander et al. <sup>31</sup>	COX-2 inhibition directly responsible for downstream production of PGE2	Prostaglandin E <sub>2</sub> as a modulator of viral Infections	90 mg OD for 5 days	CNS Headache Heart: Chest pain, high blood pressure, and fluid retention Metabolic: Taste disturbances, mouth ulcer, loss of appetite, and weight loss

## MATERIALS AND METHODS

### Study Overview

The study was conducted by the Department of Critical Care Medicine in a tertiary care hospital located in Pune, India. The study was approved by the institutional ethics committee (IHR\_2020\_APR\_NM\_361) and due to the nature of the retrospective chart review, the need for informed consent from individual patients was waived.

### Criteria for Patient Selection

All patients who presented with symptoms of fever, cough, breathlessness, myalgia or fatigue, and travel history were tested as per the government policy<sup>7</sup> and admitted to the hospital. Patients who tested positive by RT-PCR for COVID-19, shortness of breath at rest or with exercise (6-minute walk test), and room air saturation less than 94% requiring oxygen less than 4 L/minute were admitted to the monitored isolation ward while those requiring oxygen support more than 4 L/minute were admitted to the intensive care unit (ICU). Five IM drugs, namely tocilizumab,<sup>14,15</sup> colchicine,<sup>17</sup> hydroxychloroquine,<sup>24,25</sup> methylprednisolone,<sup>18</sup> and etoricoxib<sup>31</sup> were prescribed in various combinations to these hypoxic patients as per the discretion of the treating physician. The patients were grouped into seven mutually exclusive groups for analysis with a maximum of three drugs in each group for ease in collection of data. Ceftriaxone and azithromycin were given to majority of our patients for the first 3–5 days. Patients were discharged from the ICU and hospital based on a predecided government policy.<sup>7</sup>

### Laboratory Confirmation

Confirmation of COVID-19 was done through real-time reverse transcriptase-polymerase chain reaction (RT-PCR) at National Institute of Virology, Pune, on nasopharyngeal and oropharyngeal samples collected by trained staff as per the government policy.

### Inclusion Criteria

COVID RT-PCR-positive patients aged more than 18 years who required oxygen therapy within 72 hours of their hospital admission.

### Exclusion Criteria

- Patients who were already on steroids or immunosuppressant drugs for any other clinical condition.
- Imminent death within 24 hours of hospital admission (more than two organ failures on admission).

### Data Source

Clinical data pertaining to admitted patients meeting the inclusion criteria were collected between March 22 and May 31, 2020, inclusive of those dates, and the clinical outcomes were monitored till June 7, 2020, the final date of follow-up. Demographics, clinical and laboratory data on admission and the subsequent trends, mode of respiratory support (invasive mechanical ventilation, noninvasive mechanical ventilation, oxygen mask), fraction of inspired oxygen (FiO<sub>2</sub>), arterial partial pressure of oxygen (PaO<sub>2</sub>), PaO<sub>2</sub>/FiO<sub>2</sub> ratio, and IM agents administered were collected by a team of two senior registrars from the electronic medical records and were entered into a computerized database. The collected data were analyzed and interpreted by two independent intensivists. The clinical team provided clarification on missing or redundant data.

### Data Analysis

Radiological assessment included analysis of chest radiographs and bedside ultrasonography (USG). Laboratory tests were performed

as per the clinical needs of the patients at discretion of treating physicians. Electrocardiogram (ECG) and chest radiographs were analyzed by the registrars and confirmed by intensivists. Patients with a baseline QT interval (QTc) more than 500 ms were not administered hydroxychloroquine (HCQ). Data pertaining to coexisting conditions were ascertained from documents/history.

All the authors have checked for the correctness of the data and have reviewed the manuscript and vouch for the correctness, accuracy, and completeness of the data and for the adherence of the study to the protocol submitted.

### Study Definitions

The date of disease onset was defined as the day when the symptoms of fever, cough, breathlessness, myalgia, or fatigue were noticed.

Patients were grouped into mild, moderate, and severe acute respiratory distress syndrome (ARDS) based on calculation of PaO<sub>2</sub>/FiO<sub>2</sub> ratios<sup>8</sup> (Table 2).

QT prolongation was considered if QTc was more than 470 ms in males and 450 ms in females.<sup>9</sup> Lymphocytopenia was defined as the absolute lymphocyte count of less than 1000/mm<sup>3</sup>.<sup>10</sup>

### Study Outcomes

In-hospital mortality, requirement for mechanical ventilation, and discharge or present status of the patients as of June 7, 2020, were recorded separately and also presented on a predefined ordinal scale (Table 3). Length of stay in hospital and ICU were also determined.

### Statistical Analysis

Statistical analysis was carried out with the help of IBM SPSS statistics for Windows, version 23, (IBM Corp., Armonk, NY, USA). The data were analyzed using descriptive statistics. No statistical sample size calculation was performed a priori. Continuous variables were presented as median and interquartile range (IQR), and categorical variables were expressed as counts and percentages. The Chi<sup>2</sup> test was used for categorical variables as appropriate. The multivariate regression analysis was carried out to identify independent variables as predictors. All statistical tests were two-tailed, and statistical significance was defined as  $p < 0.05$ . No imputation was made for missing data. As our study population was not derived from random selection, the analysis was not adjusted for multiple comparisons and given the possibility of type I error, all statistics are deemed to be descriptive only.

**Table 2:** PaO<sub>2</sub>/FiO<sub>2</sub> ratio

P/F ratio	Category
>300	Normal
≤300 (mild)	Mild
≤200 (moderate)	Moderate
≤100 (severe)	Severe

**Table 3:** Ordinal scale

1	Discharge to home
2	Hospitalized not requiring oxygen but ongoing care for COVID-related or other medical conditions
3	Hospitalized requiring oxygen
4	Hospitalized requiring noninvasive ventilation or high-flow oxygen devices
5	Hospitalized on invasive mechanical ventilation
6	Death

**RESULTS**

**Baseline Characteristics on Admission**

During the study period, a total of 415 confirmed COVID-19 patients were admitted to our hospital. Based on the clinical condition and oxygen requirements, 134 patients who met the inclusion criteria were admitted to monitoring unit or ICU while the rest to the isolation wards.

The median age of the patients in our study was 55.6 years (range 20–89 years) and 68% were men. Fever was the presenting symptom in 82.1% of patients while shortness of breath (77.2%), cough (61.9%), myalgia/fatigue (28.4%), gastrointestinal symptoms (13.4%), and sore throat (7.5%) were the other presenting complaints. Approximately 72% of our study population had at least one comorbidity; diabetes (44%) and hypertension (46%) were the most common comorbidities observed (Table 4B).

Lymphocytopenia was seen in 51.1% and thrombocytopenia in 13.6% of patients. Inflammatory markers interleukin 6, ferritin, and D-dimer were done in selected patients as per the discretion of the treating physician. The number of patients tested and median values are depicted in Table 4C.

About 86% of the chest radiographs were abnormal with 78.2% showing involvement of zones 1–4, while 7.5% had involvement of zones 1–4 and lobar pneumonia. Bedside lung ultrasound reports were available for 46 patients; 63% had B lines and 23.9% had both B lines and subpleural consolidation (Tables 4D and E).

About 60% of patients had a PaO<sub>2</sub>/FiO<sub>2</sub> ratio less than 300 on admission. The PaO<sub>2</sub>/FiO<sub>2</sub> ratio ≤150 was seen in 50% of the patients with comorbidities as compared to 31.6% of patients without comorbidities [(*p* = 0.040, OR 1.2 (95% CI 1.0–1.5)] (Table 4F).

Respiratory devices required by these patients (within 72 hours of admission) have been depicted in the Table 4G.

**Immunomodulatory Drugs**

- Distribution of IM drugs used (Table 5A): The IM drugs were given to patients in various combinations as per the discretion of the treating physicians. Twenty-three patients could not be placed into any mutually exclusive groups. Hydroxychloroquine (*n* = 119) and low-dose methylprednisolone (*n* = 116) were given to majority of the patients.
- Outcome (Table 5B): Higher percentage of mortality and ventilator requirements were seen in patient group IV (HCQ+ MPS+ tocilizumab) while patients in group V (only HCQ) had the lowest.
- IM drugs and hospital stay (Table 5C): The mean ICU and hospital stay was longer for patients in group IV (HCQ + MP + tocilizumab) as compared to other groups.
- Interval between symptom onset and initiation of IM drugs (Table 5D): Out of 94 patients who were given IM drugs within 5 days of symptom onset, 63.8% were discharged home and 28.7% died. While 77.5% out of 40 patients who were given IM drugs after 5 days were discharged home and 22.5% died.

**Mortality Statistics**

The mean age of patients who died was 58.8 ± 12.0 years with 61% being men and 80.5% had more than one associated comorbid condition (Flowchart 1).

The proportion of patients with hypertension was significantly higher among the patients who died (Table 6).

**Table 4:** Baseline characteristics on admission

A. Demographics			
Characteristics	N	%	
Men	91	67.9	
Age in years, median	55.6 years	(Range 20–89 years)	
B. Coexisting conditions			
Comorbidity	N	%	
Diabetes mellitus	59	44	
Hypertension	62	46	
Ischemic heart disease	19	19	
Obesity	16	16	
Chronic obstructive lung disease/interstitial lung disease	9	9	
Chronic kidney disease	4	4	
Cancer	1	1	
C. Laboratory			
Parameters	N	Median	
White blood cell count/mm <sup>3</sup>	132	7420 (4945–10,810)	
Creatinine in mg%	130	0.99 (0.78–1.58)	
Nucleotide oligomerization domain (NOD)-like receptor (NLR)	134	5.93 (3.2–9.8)	
IL-6 pg/mL	24	62.8 (18.5–100.5)	
C-reactive protein mg/L	105	118 (56.3–181)	
Ferritin ng/mL	57	384.4 (135.4–936.4)	
D-dimer ng/mL	70	1015.3 (524.5–1527.2)	
D. Chest X-ray ( <i>n</i> = 133)*			
Finding	N	%	
Normal	19		
Zone 1–4	104	78.2	
Zone 1–4, lobar pneumonia	10	7	
E. USG Chest ( <i>n</i> = 46)			
Finding	N	%	
Normal	5	10.9	
B lines	29	63	
B lines + subpleural consolidation	11	23.9	
Subpleural consolidation	1	2.2	
F. Proportion of patients with P/F ratios ( <i>n</i> = 116)			
P/F ratio category	Patients on admission <i>n</i> (%)	Patients with worst P/F ratio <i>n</i> (%)	
≤300 (mild)	42 (31.3)	30 (22.4)	
≤200 (moderate)	36 (26.9)	22 (16.4)	
≤100 (severe)	18 (13.4)	48 (35.8)	
≥300 (normal)	20 (14.9)	16 (11.9)	
G. Respiratory assist devices used within 72 hours of admission			
Respiratory assist device	<i>n</i>	%	
Nasal prongs	58	43.3	
O <sub>2</sub> mask	15	11.2	
Nonbreathing mask	40	29.8	
High-flow nasal oxygen	15	11.2	
Invasive mechanical ventilation	6	4.5	

\*Zones on chest X-ray: Zone 1, apical zone-above the clavicle; Zone 2, between the clavicle and cardiac silhouette; Zone 3, midzone: level of hilar structures; Zone 4, bases

**Table 5: Immunomodulatory drugs**

A. Distribution of IM drugs used (n = 134)			
Group	IM drug group	N	%
I	HCQ + MP	42	31.3
II	HCQ + MP + colchicine	39	29.1
III	HCQ + MP + etoricoxib	4	3.0
IV	HCQ + MP + tocilizumab	5	3.7
V	HCQ	12	9.0
VI	MP*	9	6.7
VII	Others**	23	17.2
	Total	134	100

**B. Outcome**

Group	Drug	Mortality			Requirement of mechanical ventilation	
		Given	Died	%	Req. vent	%
I	HCQ + MP	42	10	23.8	12	28.6
II	HCQ + MP + colchicine	39	11	28.2	15	38.5
III	HCQ + MP + etoricoxib	4	0	0	0	0
IV	HCQ + MP + tocilizumab	5	2	40	2	40
V	HCQ	12	2	16.7	1	8.3
VI	MP*	9	3	33.3	3	33.3
VII	Others**	23	8	34.8	7	30.4

**C. Analysis of IM drugs distribution vs mean ICU and hospital stay**

Group	IM drug	Mean ICU stay (n = 65)		Mean hospital stay (n = 134)	
		n	Mean	n	Mean
I	HCQ + MP	16	3.50	42	10.67
II	HCQ + MP + colchicine	31	6.39	39	12.77
III	HCQ + MP + etoricoxib	0	0	4	11.50
IV	HCQ + MP + tocilizumab	2	15.00	5	15.60
V	HCQ	4	3.25	12	10.17
VI	MP*	4	2.50	9	9.00
VII	Others**	12	6.92	23	14.52

**D. Interval between symptom onset to IM drug initiation**

Parameter	Interval <5 days (n = 94)	Interval ≥5 days (n = 40)
Ordinal scale		
Well and discharged home	60 (63.8)	31 (77.5)
Hospitalized, not requiring O <sub>2</sub>	2 (2.1)	0 (0)
Hospitalized, requiring NIV or high-flow O <sub>2</sub> devices	1 (1.1)	0 (0)
Hospitalized, requiring invasive mechanical ventilation	4 (4.3)	0 (0)
Death	27 (28.7)	9 (22.5)

HCQ, hydroxychloroquine; ICU, intensive care unit; MP, methylprednisolone; NIV, noninvasive ventilation

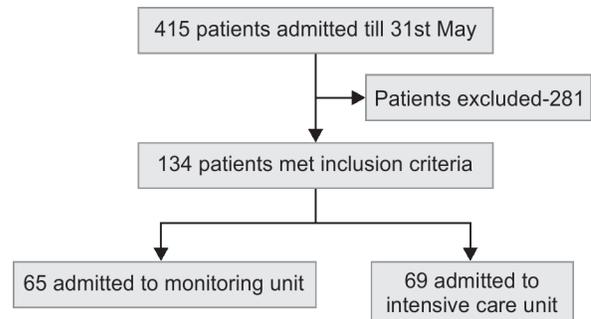
\*Low dose

\*\*Contains drug combinations not present in any of the predefined groups

**Table 6: Mortality statistics**

Parameter	Died n (%)
Coexisting conditions	
Diabetes mellitus	17 (47.2)
Hypertension	23 (63.9)
Ischemic heart disease	6 (16.7)
Obesity	7 (19.4)
Respiratory parameters	
P/F ratio <200	34 (94.4)
Invasive ventilation	36 (100%)
Laboratory parameters	
Normal lymphocyte count	12 (33.3)
Highest s. creatinine >1.2 mg%	28 (77.8)
Thrombocytopenia	5 (13.9)
Total	36 (100)

**Flowchart 1: Patient inclusion and disposition on admission**



A multivariate regression analysis was carried out based on the available independent variables from clinical and laboratory data, to identify factors predicting mortality. A model was constructed using significant predictors from both groups together (Table 7).

It was found that SpO<sub>2</sub> <80%, respiratory rate >22/minute, PaO<sub>2</sub>/FiO<sub>2</sub> <200, white blood cell count >12,000/mm<sup>3</sup>, absolute lymphocyte count <1000/mm<sup>3</sup>, and the highest serum creatinine >1.2 mg% were significant predictors.

The overall model fit was R<sup>2</sup> = 46.8%.

**Outcomes and Adverse Events**

None of the 134 patients were lost to follow-up during the study. A primary endpoint (discharge or death) occurred in 95.6% of patients. About 68.7% of patients were discharged home, while 26.9% died and rest were still at hospital undergoing various stages of treatment till the time of analysis of data. The cause of death is depicted in Table 8B. About 50% of patients had hyperglycemia, 20.1% had QTc prolongation, and secondary bacterial infection was seen in 13.4% of patients while 40.3% patients had no known adverse events documented during the course of study (Table 8C).

**DISCUSSION**

This retrospective study would be to our knowledge the first study in India and among other resource-limited countries that presents a wide spectrum of descriptive and analytical data of hypoxic COVID-19 patients treated with a varied combination of IM drugs. During the course of our study, we noted that five variables among the clinical and laboratory parameters were found to be significant



**Table 7:** Significant predictors

Model	Multivariate regression analysis				
	Unstandardized coefficients		Standardized coefficients		p value
	B	Std. error	Beta	t	
(Constant)	-0.092	0.205		-0.450	0.654
Highest S. creatinine, mg%	0.315	0.068	0.342	4.628	0.000
SpO <sub>2</sub> <80%	0.278	0.080	0.269	3.455	0.001
PF ratio <200	0.164	0.072	0.179	2.272	0.025
Absolute lymphocyte count <1,000/mm <sup>3</sup>	0.163	0.065	0.181	2.518	0.013
WBC more than 12,000/mm <sup>3</sup>	0.195	0.087	0.171	2.247	0.027

Dependent variable: mortality

**Table 8:** Outcome data

A. Outcome ordinal scale (at the time of going to analysis)		
Scale order	Ordinal scale description	Patients n (%)
1	Well and discharged home	91 (68.7)
2	Hospitalized, not requiring O <sub>2</sub>	2 (1.5)
3	Hospitalized, requiring NIV or high-flow O <sub>2</sub> devices	1 (0.7)
4	Hospitalized, requiring invasive mechanical ventilation	4 (3)
5	Death	36 (26.9)

B. Causes of death (n = 36)	
Cause of death	n (%)
Respiratory	19 (52.8)
Multiorgan failure + sepsis	15 (41.7)
Cardiac	2 (5.6)
34 (94.4%) died in the intensive care unit	

C. Adverse events (n = 134)	
Adverse event	n (%)
High sugars	67 (50)
QTc prolongation	27 (20.1)
Acute coronary syndrome	5 (3.7)
Secondary bacterial infection	18 (13.4)
Shock	20 (14.9)
None	54 (40.3)

predictors of mortality. No single IM drug or in combination with others was associated with outcome.

Immunomodulation remains to be the mainstay of treatment based on our previous experiences with SARS and H1N1 pandemics in the absence of any effective direct antiviral drug therapy.<sup>11,12</sup> Siddiqi et al.<sup>13</sup> proposed a three-stage classification of COVID-19 illness and suggested starting of anti-inflammatory therapies such as steroids from stage IIB when hypoxia develops. Majority of our patients received hydroxychloroquine and methyl prednisolone. Owing to the nonuniformity in groups of IM drugs administered and lack of control groups, only descriptive analysis was possible in our study. However, we noted a longer ICU/hospital stay, higher percentage of mortality, and ventilator requirements in patients receiving a combination of tocilizumab along with HCQ and methyl prednisolone. This is contrary to the results from case control studies by Klopfenstein et al.<sup>14</sup> and Guaraldi et al.<sup>15</sup> that showed

significantly less percentage of mortality in the tocilizumab group. The observations of our study may be explained by the fact that tocilizumab was administered to a very small proportion of patients. On the other hand, the length of the hospital/ICU stay in our patients is comparable to study by Tariq Kewan et al.,<sup>16</sup> which showed longer duration of hospital stay in the tocilizumab group.

In a study conducted by Spyridon G. Deftereos et al.,<sup>17</sup> no statistically significant outcomes were observed in participants who received colchicine along with HCQ, azithromycin, and tocilizumab.

Two recent studies by Fadel et al.<sup>18</sup> and Fernández-Cruz et al.<sup>19</sup> reported a beneficial effect on mortality in patients treated with steroids in early phase where the interval between symptom onset to IM drug initiation was a median value of 8 and 10 days, respectively. Most of our patients were initiated with IM drugs before 5 days of onset of illness, which is much earlier when compared to the above studies.

More than half of our patients were admitted to the ICU. About 32% (n = 43) of our patients required mechanical ventilation during the hospital stay. This percentage is higher when compared to the earliest statistics from Wuhan, China<sup>20</sup> (16%) and lower when compared to Lombardy, Italy<sup>21</sup> (88%) and fairly comparable to other studies from Wuhan, China (30%).<sup>22</sup>

Considering the fact that 96% of our patients had attained the primary endpoints, the mortality rate in our study was very low, which is similar to most of the statistics from New York,<sup>23</sup> Lombardy,<sup>21</sup> and Wuhan.<sup>20</sup> Our patients were much younger and the proportion of hypertensives was significantly higher in those who died. In-hospital mortality rate of 26.9% and a higher mortality (83.7%) in patients who were mechanically ventilated were comparable to results from different regions of the world. It is difficult to compare mortality rates between studies because the outcomes can be affected by healthcare systems, resources, patient demographics, and prevalence of comorbidities. Mortality rates might be higher in studies conducted over long-term or at a different epidemiological stage.

Among adverse events, our incidence of QTc prolongation (20%) was higher than other studies where HCQ was used. This could be because of our threshold of QT prolongation being >450 ms in males and 470 ms in females as compared to other studies and also the fact that most of our patients were coadministered azithromycin.

A study by Borba et al.<sup>24</sup> in patients suffering from SARI COVID-19, looking at high-dose vs. low-dose HCQ therapy found QT prolongation in 18% of high-dose compared to 11% of low-dose group pointing toward dose-related toxicity. Chorin et al.<sup>25</sup>

showed that in 84 patients treated with hydroxychloroquine and azithromycin, QTc prolonged maximally from baseline in 11% of patients, representing the high-risk group for arrhythmia.

The incidence of hyperglycemia (50%) and clinically significant secondary bacterial infections requiring escalation of antibiotics was comparable with other studies.<sup>26</sup>

Recent studies<sup>27-31</sup> have reported an association between age, high WBC counts, and absolute neutrophil value with low lymphocyte count (neutrophil-lymphocyte ratio) and worse outcomes.

In our study, we found that the following five variables (SpO<sub>2</sub> <80%, RR >22/minute, PaO<sub>2</sub>/FiO<sub>2</sub> <200, WBC >12,000/mm<sup>3</sup>, ALC <1000/mm<sup>3</sup>, sr. creatinine >1.2 mg%) were found to be significant predictors of mortality in our patients. Even though these variables have not been validated as a scoring system, the need of the time is to develop a scoring system based on ubiquitous clinical findings and laboratory biomarkers for early triage and disposition especially in resource-limited settings.

### Limitations

Our study has several limitations. First, this was a retrospective observational study with all its inherited biases. Second, the data were collected from electronic medical health record database, thereby precluding detailed information about the patients demographics and baseline medications. Third, the nonuniformity in the distribution of the IM agents, limited investigations being done because of cost constraints, high heterogeneity observed, due to the participants' inclusion criteria as well as by the studies design making the data redundant for comparative analysis. Fourth, as the follow-up time of our study was relatively short compared to the course of the disease, it could change the outcome variables studied.

### Strengths

Our study would be one of its kind comparing groups of IM drugs and their outcomes in resource-limited settings. It also provides a wide spectrum of demographic data of critical COVID-19 patients from our country and their outcomes in a tertiary level hospital in India.

### Implications for Future Research

Larger trials with a more robust study design, randomized control trials comparing the different IM agents in regards to important clinical outcome variables. Construction and validation of outcome predictor scores based on easily available clinical and laboratory variables to guide the clinicians for better allocation of the scarce medical resources especially in resource-limited settings.

### CONCLUSION

In our study of critically ill hypoxic COVID-19 patients, five different IM agents were used in varied combinations. The requirement of mechanical ventilation was seen in 32%, in-hospital mortality rate was 26.9%, and a higher mortality of 83.7% among the mechanically ventilated patients. Five variables among the clinical and laboratory parameters were found to be significant predictors of mortality.

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