Original Research Article

Clinical characteristics and laboratory findings of mild to moderate covid-19 cases admitted to tertiary care hospitals and their association with adverse outcomes

Jain Ashish[1*], Sharma Krishna Kumar[2*], Jain Srishti[3], Kalia Anchin[4], Malawat Aman[5]

[1]Associate Professor& Director, Critical Care Medicine, Mahatma Gandhi Medical College & Hospital, Jaipur, Rajasthan, India
[2]Senior Consultant, Pulmonary Medicine, EHCC Hospital, Jaipur, Rajasthan, India
[3]Associate Professor& Add. Director, Critical Care Medicine, Mahatma Gandhi Medical College & Hospital, Jaipur, Rajasthan, India
[4]Professor, General Medicine, Mahatma Gandhi Medical College & Hospital, Jaipur, Rajasthan, India
[5]Senior Resident, Critical Care Medicine, Mahatma Gandhi Medical College & Hospital, Jaipur, Rajasthan, India

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Abstract

Introduction: The symptoms of COVID-19 are highly variable, classifying cases diagnosed with coronavirus disease (COVID-19) according to their clinical characteristics and associated outcomes is important for management of this disease. **Methods:** Clinical characteristics of mild-moderate COVID 19 was studied at tertiary care facilities in India. A total of 668 patients were analysed, their demographics, disease, clinical characteristics and laboratory parameters were recorded and the association of these factors with adverse outcomes was analysed. **Results:** A total of 668 patients were included in this study, of those 69 % were males and the overall mean age was 50.7 13.2 years. Comorbidities were present in 530 patients and 32 patients were smokers, except 2 patients all were symptomatic at the time of admission. During hospital stay, eventually 124 (18.5%) required high flow nasal cannula , 71 (10.6%) required ventilator support and 5 (0.7%) succumbed to death. Majority of patients i.e., 70% were discharged without any adverse outcomes. The factors significantly associated with adverse outcomes were age, comorbidity, duration of stay, elevated CRP, SGPT, SGOT, INR, NT-proBNP, IL-6, ferritin, D-Dimer, and LDH; low platelet count and hemoglobin. **Conclusion:** Clinical characteristics, hematological, inflammatory markers and biochemical parameters can predict disease progression and adverse outcomes.

Keywords: Clinical characteristics, demographics, biochemical parameters, COVID 19.

Introduction

COVID-19 is a highly infective acute respiratory disease caused by a novel coronavirus SARS-CoV-2, which was first identified in Wuhan, China, in December 2019. Epidemiological and virological studies show that transmission occurs through respiratory droplets from symptomatic people to others by close contact, by direct contact with infected persons, or by contact with contaminated objects and surfaces[1-4]. The incubation period for COVID-19 is, on average, 5–6 days, but may range up to 14 days. The symptoms of COVID-19 are highly variable, ranging from no or minimal symptoms to significant hypoxia with complications. Hence, the cases are classified into asymptomatic, mild, moderate, severe and critical. Most people with COVID-19 develop only mild (40%) or moderate (40%) disease, approximately 15% develop severe disease that requires oxygen support, and 5% have critical disease with complications which could be fatal such as respiratory failure, acute respiratory distress syndrome (ARDS), sepsis and septic shock, thromboembolism, and/or multiorgan failure, including acute kidney injury and cardiac injury[5].

Classifying cases diagnosed with coronavirus disease (COVID-19) according to their clinical characteristics and associated outcomes is integral to management of this disease.

*Correspondence
Dr. Jain Ashish
Associate Professor& Director, Critical Care Medicine, Mahatma Gandhi Medical College & Hospital, Jaipur, Rajasthan, India

Several studies describing the clinical features and outcomes of retrospective cohorts of patients with COVID-19 have recently been published. The mild or moderate cases should be isolated to prevent further transmission and should be admitted to the hospital to prevent further progression of the disease, severe and critical patients require more attention and need hospitalization due to poor outcomes[6]. However, the limited capacity of designated hospitals for COVID 19 makes the prevention and treatment of COVID-19 challenging.

The clinical presentation and outcomes of patients with COVID-19 have been variable in different countries[7-14]. Therefore, it is important to analyse and document the clinical characteristics of this disease in the local population. In this study, we aimed to describe the clinical characteristics of 668 hospitalized mild-moderate patients and evaluate their association with clinical outcomes admitted to tertiary care facilities in India.

Methods

Study design and participants

This was a prospective observational study reviewed and approved by the Institutional Ethics Committee. Written informed consent from the participant/ participant's kin was waived off. During the period of June 1st, 2020 to September 30th, 2020, 668 RT-PCR positive confirmed mild to moderate cases of SARS-CoV2 who were admitted to Mahatma Gandhi medical college and hospital, Jaipur and EHCC hospital, Jaipur were enrolled in this study. The diagnosis of COVID-19 was made according to the WHO interim guidance for clinical management of COVID 19, 2020. The outcome information of these patients was collected until September 30th, 2020, including discharged, and death.

Data collection

The clinical data (including basic information, clinical symptoms and signs, history, comorbidities, treatment and outcomes) were obtained by experienced clinicians. Laboratory parameters were summarised by incorporating the documentation or description in medical charts.

Outcome measures

The main outcome measured in this study were high flow oxygen requirement, ICU admission and in-hospital mortality.

Statistical analysis

The continuous variables showed normal distribution are expressed as the mean and standard deviation and were compared with ANOVA. The categorical variables are presented as counts (percentages) and were compared with chi-square tests. All statistical analyses were performed with Excel stst, and P value less than .05 was considered statistically significant.

Results

Demographics and disease characteristics

A total of 668 patients were included in this study, of those 69 % were males and the overall mean age of our study population was 50.7 □ 13.2 years. Comorbidities were present in 530 patients, of which hypertension was the most common comorbidity observed and 32 patients were smokers. Except 2 patients all were symptomatic at the time of admission, common symptoms were fever (266,44.7%), cough 188(31.8%) and dyspnoea 106(17.9%).

Most patients were treated with supportive care and required only symptomatic treatment. However, HCQ was prescribed to 100 (15 %) patients, remedesevir was administered to 314 (47 %) patients and 102 (15.3 %) received favipiravir. Tocilizumab was administered to 85 (12.7%) patients. 23 patients required renal replacement therapy. On admission, vasopressors were required in 15 (.02%) patients, oxygen support in 214 (32%) patients and non-invasive ventilation support in 30 (4.5%) patients. During hospital stay, eventually 124 (18.5%) required high flow nasal cannula , 71 (10.6%) required ventilator support and 5 (0.7%) succumbed to death. Majority of patients i.e., 70% were discharged without any adverse outcomes.

The factors significantly associated with adverse outcomes were found to be age (p=0.015), presence of comorbidities (p=0.000), duration of stay (p=0.000) and elevated CRP (p=0.000), SGPT (p=0.000), SGOT (p=0.000), INR (p=0.000), NT-proBNP (p=0.000), IL-6 (p=0.000), ferritin (p=0.000), D-Dimer (p=0.000), platelets (p=0.002), and hemoglobin (p=0.000) (Table 2,3). Duration of stay was also significantly longer in patients with adverse outcomes (p=0.000). Also, patients treated with HCQ, remdesevir, tocilizumab, anticoagulants, high and low dose steroids and antifungals, suffered less adverse outcomes like need for high flow oxygen or ventilator or death.

Table 1 summarizes the demographic and disease characteristics of patients.

Variables		Frequency/proportion/mean±SD
Age		50.74 ± 15.15
Sex	Male	420
	Female	172
BMI		26.39 ± 4.58
Smoking	Yes, Currently	9
	Ex-smoker	7
	No, Never	562
Co-morbidity	Yes	403
	No	191
	Asthma	3
	Hypothyroidism	101
	Chronic Renal Disease	32
	CAD/IHD	65
	DM	205
	Hypertension	288
	Malignancy/Cancer	5
	COPD	3
	Cerebrovascular Disease	3
	Other	22
Symptoms	Yes	592
	No	2
	Fever	491
	Chills	14
	Shortness of Breath	209
	Cough	368
	Conjunctival Congestion	18
	Diarrhea	15
	Fatigue	14
	Headache	69
	Nausea and/or Vomiting	17
	Loss of Taste	4
	Myalgia/ Arthralgia	66
	Sore Throat	77
	Anosmia	5
	Nasal Congestion	2
	Hemoptysis	2
	Sputum Production	3
	Other	88

Table 2: Association of gender and relevant history of patients with clinical outcomes.

Variables		Adverse Outcome				Chi square (df)
		No (n= 468)	Oxygen requirement (n = 124)	Ventilator support (n = 71)	Death (n = 5)	
Sex	Male	350	70	40	1	27.394 (3)
	Female	118	54	31	4	
Smoking	Yes	17	11	4	0	6.265 (3)
	No	451	113	67	5	
Co-morbidity	Yes	351	110	65	4	18.478 (3)
	No	117	14	6	1	
Symptoms at the time of admission	Yes	466	124	71	5	
	No	2	0	0	0	
Renal replacement therapy	Yes	1	16	6	0	53.594 (3)
	No	467	108	65	5	
Vasopressor on admission	Yes	13	0	2	0	3.673 (3)
	No	455	124	69	5	
Oxygen support on admission	Yes	76	79	56	3	184.103 (3)
	No	392	45	15	2	
NIV support on admission	Yes	12	5	13	0	35.956 (3)
	No	456	119	58	5	

Table 3: Association of treatment given on admission and clinical outcomes.

Treatment given		Adverse Outcome				Chi square (df)
		No (n= 468)	Oxygen Requirement (n = 124)	Ventilator support (n = 71)	Death (n = 5)	
HCQ	Yes	83	13	4	0	10.514 (3)
	No	385	111	67	5	
Low dose steroid	Yes	267	49	27	1	20.049 (3)
	No	201	75	44	4	
High dose steroid	Yes	176	66	42	4	21.180 (3)
	No	292	58	29	1	
LMWH/ fondaparinux	Yes	174	111	54	3	127.39 (3)
	No	294	13	17	2	
Remdesivir	Yes	190	77	43	4	26.47 (3)
	No	278	47	28	1	
Favipiravir	Yes	70	22	9	1	1.077 (3)
	No	398	102	62	4	
Tocilizumab	Yes	14	39	29	3	139.699 (3)
	No	454	85	42	2	
Antifungals	Yes	14	15	11	2	35.58 (3)
	No	454	109	60	3	
Oseltamivir	Yes	4	1	0	0	0.647 (3)
	No	466	123	71	5	

Table 4: Association of clinical characteristics and laboratory parameters with clinical outcomes.

Variables		Adverse Outcome							
		No (n= 468)		Yes					
				Oxygen requirement (n = 124)		Ventilator support (n = 71)		Death (n = 5)	
Mean	Standard deviation	Mean	Standard deviation	Mean	Standard deviation	Mean	Standard deviation		
Age		50.72	13.58	50.7	13.5	56.13	13.68	55.6	22.9
BMI		26.23	5.36	26.65	2.85	26.6	3.3	25.78	4.94
Temperature at admission (°F)		98.85	0.89	98.85	0.90	98.17	5.49	99.1	0.79
Duration of stay in hospital		5.7	3.4	9.8	2.8	9.5	4.6	6.6	3.4
Laborat	Hemoglobin	12.48	2.01	11.04	1.45	10.98	1.95	8.87	1.6
	TLC	10019.24	7452.34	18676.7	24959.08	18522.66	27063.64	19257.5	19019.03
	Neutrophills	69.5	19.29	71.05	16.62	74.6	17.5	80.77	16.78
	Lymphocy	21.75	13.18	23.07	13.48	20.53	14.28	20.78	15.42

o r y p a r a m e t e r s	te								
	Platelets	246769.9	103500	213825.3	84901.75	213994	93739	269250	70839.61
	D Dimer	1049.29	1735.23	2164.19	3413.04	2888.08	4631.57	2425.66	1798.45
	Ferritin	467.76	456.43	438.54	515.06	659.66	538.32	1188.8	827.35
	LDH	296.17	276.78	353.4	155.62	375.87	167.08	589.33	54.78
	IL-6	109.34	429.91	68.82	61.11	598.02	1349.87	80.78	20.54
	NT-ProBNP	2301.97	6712.76	12598	13821	6498.35	12072.17	509.4	429.18
	INR	1.22	0.22	1.26	0.2	1.3	0.22	1.14	0.22
	SGOT	48.67	56.44	62.41	20.35	69.73	69.75	74.33	16.80
	SGPT	36.33	25.6	49.40	20.50	45.54	21.79	46	5.29
	S Creatinine	2.32	10.26	1.65	3.99	2.71	6.42	1.4	0.88
	CRP	11.8	13.68	35.65	45.09	29.18	23.89	73.67	65.27
	Procalcitonin	1.82	8.05	0.69	0.75	0.59	0.6	0.56	0.62

Discussion

Our study was designed to analyze the clinical findings and outcomes of mild-moderate patients in tertiary care hospitals. In this study, we found an association between several risk factors and clinical outcomes. We found significant association of age, gender and comorbidity with adverse outcomes. Our study also found that anemia, elevated Il 6, CRP, ferritin, D-dimer, and liver enzymes were associated with adverse outcomes indicating that patients with these characteristics should receive extra attention. Studies have revealed that most of the patients infected with SARS-CoV-2 had mild or moderate infections. These patients with mild-moderate illness require supportive treatment generally, however a may require intensive care on increasing severity. If these patients are not effectively treated or isolated in the early stages, their activities further contributes to the spread of the disease in the community.

Only 30.9 % of the patients were female, which is lower but consistent with other studies which also observed that women had a lower admission rate than men[15-16]. As observed in previous studies, males were associated with more adverse outcomes. The mechanisms underlying the reported gender differences are not well understood at this time. Some conclusions can be made based on existing awareness of gender disparities in respiratory virus diseases. Some lifestyles, such as smoking, are most likely related to COVID-19's negative development and negative outcomes in males[17]. Males have higher levels of pro-inflammatory cytokines and chemokines. Males have a higher expression of the core cytokine storm, IL-6 receptor, in lung epithelial cells, meaning that males are more vulnerable to cytokine storm, which may contribute to COVID-19 degradation[18-20].

Similar to several studies, older age is associated with severe outcomes, the explanation for this may be that elderly patients' nutritional status and immune function are also low, which may lead to immune system damage and extreme pneumonia, raising the risk of death. In our study, comorbidities are significantly associated with adverse outcomes[21-23]. Blood pressure is linked to the presence of the ACE2 receptor. When compared to patients without hypertension, patients with hypertension can have lower levels of ACE2 receptors. The ACE2 receptor is used by SARS-CoV-2 to infect cells. The protective effect of ACE2 in acute lung injury was verified by Imai et al., who found that it is strongly expressed in the lung. When SARS-CoV-2 infects the lungs, it reduces the numbers and function of ACE2 protein in the lungs, resulting in acute lung failure. ACE2 receptor expression will be reduced once they are infected with SARS-CoV-2. Hypertension is one of the first symptoms of COVID-19-positive hypertension patients. After respiratory failure and multiple organ failure, COVID-19 patients can develop shock and hypotension, indicating that they have progressed to the serious and critical level[24]. Hyperglycemia and other metabolic disorders are common in diabetic patients. They are vulnerable to infections, when diabetic patients become infected, it not only worsens their basic illnesses, but it also puts them at risk of multiple organ failure. Furthermore, type 2 diabetes is linked to decreased ACE2 activity[20]. In patients with COVID-19, myocardial damage is also frequent. Acute myocardial injury has been described in various ways, including a rise in cardiac enzymes and/or electrocardiographic irregularities[25]. These results add to the increasing body of evidence that baseline comorbid diseases should be considered when assessing prognosis in COVID-19 patients.

Our study also found that anaemia, low platelet count, elevated Il 6, ferritin, D-dimer, liver enzymes, CRP, LDH, NT- proBNP were associated with adverse outcomes indicating that patients with these characteristics should receive extra attention. Anaemic patients were found to have a higher risk of serious disease and mortality in many studies, the majority of which were performed in China[26-29]. Cecconi et al., on the other hand, found no correlation between anaemia and poor COVID-19 outcomes. Similarly, Yang et al. found no correlation between low Hb levels and COVID-19 outcomes in hospitalised patients in a Chinese study[30].A meta- analysis of 9 studies including 1779 COVID-19 patients with 399 (22.4%) severe cases reported that a low platelet count was associated with an increased risk of severe disease and mortality. The authors proposed that thrombocytopenic COVID-19 patients will experience disease with a higher risk of adverse outcomes during hospitalization[31].A meta-analysis including 52 studies involving 10,614 COVID19 patients concluded that ferritin was associated with poor prognosis and could predict the worsening of COVID-19 patients. The level of ferritin in severe patients was significantly higher than in non-severe patients [WMD 397.77 (95 percent CI 306.51 489.02), P.001]. Furthermore, non-survivors had a significantly higher ferritin level compared with the one in survivors [WMD 677.17 (95% CI 391.01-963.33), $P < .001$][32].According to previous studies, higher D-dimer levels are related to disease severity and significant mortality[33]. Nine studies observing the correlation between D-dimer levels and survival rates, with D-dimer levels of 0.79 and 3.78 (g/ml), respectively, 1521 patients survived and 597 died out of 2118 patients [4,7,9-15]. In addition, several studies have studied the relationship between D-dimer levels and disease severity. In 1551 patients with moderate disease, the mean D-dimer level was 0.58 (g/ml), while in 708 patients with serious disease, the mean D-dimer level was 3.55 (g/ml).

Some studies have shown that an increase in CRP levels can predict the severity of the disease, whereas other studies have found the opposite. CRP levels were found to be higher in the severe COVID-19 in a meta-analysis. Furthermore, in another meta-analysis, non-survivors had higher CRP levels than survivors, and also reported that levels of CRP increase as the severity increases[34].

Meta-analysis and meta-regression of 11 studies revealed a consistent relationship between IL-6 and COVID-19 severity, independent of age and sex. An overall random effects meta-analysis showed significantly higher serum levels of IL-6 in the severe group than in

the non-severe group with a mean difference of +23.1 pg/mL (95% CI: 12.42–33.79) and the overall effect of 4.24 (*P*-value < 0.001)[35]. Another meta-analysis of mean IL-6 concentrations demonstrated 2.9-fold higher levels in patients with complicated Covid-19 compared to noncomplicated COVID 19[36].

Many studies have suggested biochemical markers as widely available laboratory determinants to predict COVID-19 severity, similar to haematological and inflammatory parameters. According to the findings of a recent meta-analysis, severe COVID-19 cases had higher ALT, AST, and total bilirubin levels than non-severe patients (mean differences of 7.48, 12.07, 3.07)[31]. COVID-19 can cause endothelial damage, coagulation activation, and intravascular fibrin deposition as a life-threatening infectious disease. The TAT, PIC, TM, t-PAIC, PT, INR, FIB, and DD were all higher in COVID-19 as compared to the health controls, while the APTT, TT, and PLT showed no difference[37]. N-terminal pro Btype natriuretic peptide (NTproBNP) is a measure of haemodynamic stress and has been used to stratify risk in heart failure (HF) and other conditions including pulmonary embolism and pneumonia. However, there is a lack of information on natriuretic peptides in COVID 19. In a large cohort of COVID 19 patients, NTproBNP levels were higher than the recommended cutoff for HF detection in 48.5%. During admission, patients with higher NTproBNP had more bleeding, arrhythmias, and HF decompensations. Both in the entire study population and after excluding patients with HF, NTproBNP was linked to mortality. After adjusting, a multivariable Cox model reported that NTproBNP was independently correlated with mortality (hazard ratio 1.28, 95 percent confidence interval)[38]. In a meta-analysis of a total of 10,399 patients from 21 studies, elevated LDH was observed in 44 percent of the patients (34 percent–53 percent). Diabetes was linked to elevated LDH (OR 1.01 (95 percent CI 1.00 to 1.02), p=0.038) in meta-regression study, but not to age (p=0.710), male (p=0.068), or hypertension (p=0.969) and elevated LDH was linked to composite poor outcome [OR 5.33 (95 percent CI 3.90 to 7.31)] on meta-analysis[39].

In addition, our data on oxygen support and ventilation yields some intriguing suggestions. In our study 214 patients needed oxygen support and 30 needed non-invasive ventilation, out of which 138 and 18 suffered adverse outcomes, respectively, which is significant. Larger, randomised trials would be required to help distinguish between patients who may benefit from CPAP/NIV and those who should be intubated right away. It will also be interesting to see if the time at which CPAP/NIV is started has any effect on the outcome. The majority of the patients in our study were given low dose steroids and high dose steroids and both were linked to less adverse outcomes. The RECOVERY trial was the first to show that systemic corticosteroids have a beneficial survival effect in COVID-19 patients who need respiratory support (proportional mortality reduction of one fifth and one third, respectively). The dosage used in RECOVERY was 6 mg of dexamethasone given for 10 days. The living WHO guideline on drugs for COVID-19 included a strong recommendation for systemic corticosteroids in patients with serious and essential COVID-19, and a weak or conditional recommendation against systemic corticosteroids in patients with non-severe disease, i.e. those who did not need respiratory assistance, in accordance with RECOVERY[40]. While dosing and the best time to start taking the medication are still unknown, a low dose of 6 mg dexamethasone is suggested. The WHO Rapid Evidence Appraisal for COVID-19 Therapies Working Group indicated that administration of corticosteroids (in different forms and doses) in critically ill patients with COVID-19 was associated with lower 28-day all-cause mortality compared to normal treatment or placebo in a prospective meta-analysis of seven randomised clinical trials[41]. This study lacked the necessary power to determine the best treatment dosage and length, leaving this question unanswered. There is also evidence that even higher doses of COVID-19 can be considered in some cases of extreme COVID-19. To begin, high dose dexamethasone has been shown to have a beneficial mortality impact in moderate and extreme Acute Respiratory Distress Syndrome, with no increased risk of adverse events when compared to placebo[42]. Although diffuse alveolar damage has been identified in extreme COVID-19, reports indicate that Organising Pneumonia and Acute Fibrinous and Organising Pneumonia (OP/AFOP) is the most common finding in COVID-19 pathological samples.

The evidence presented in this study sheds new light on COVID-19's overall course at all in mild-moderate disease. This is in contrast to other studies, which only report on serious cases that necessitate hospitalisation. These findings suggest that patients with these risk factors should receive more attention to prevent patients' condition aggravation. Furthermore, the wide variation in clinical presentation of COVID-19, from asymptomatic to lethal, necessitates the detection and application of novel laboratory biomarkers to predict COVID-19 prognosis quickly and affordably. There are also a few limitation in our research. To begin with, patient management and treatment did not follow a strict procedure, so results may be attributed to factors other than those that were monitored. Since we did not report ventilator parameters or the use of prone positioning technique, this may be relevant for patients on CPAP/NIV or mechanical ventilation. The second point is that we have also not reported radiological findings which has evolved as an important parameter for monitoring disease evolution in these patientspatients. Finally we cannot comment on the long term outcomes, as we have not followed up patients after discharge.

Conclusion

Older age, comorbidities and some laboratory features (e.g., CRP, ferritin, IL-6, D-dimer etc) were associated with poor outcomes for these mild-moderate patients. The initial symptoms of mild- moderate patients with COVID-19 may be deceitful and warrants careful monitoring and attention

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