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Delayed admissions and efficacy of steroid use in patients with critical and severe COVID-19: an apprehensive approach

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ABSTRACT

Background Inadvertent delays in access to appropriate therapeutic interventions in high-risk group coronavirus disease 2019 (COVID-19) patients contribute to mortality in patients with severe/critical disease presentation.

Objectives The aim of this study was to determine the effect of timely admission to the hospital on mortality of patients with severe/critical COVID-19. Another secondary aspect of this study was to observe the efficacy of time-dependent use of corticosteroids on mortality of critical/severe COVID-19 patients.

Methods Clinical data of 659 patients with severe/critical COVID-19, admitted to four major tertiary care hospitals from the Islamabad-Rawalpindi region of Pakistan was retrospectively collected from a period February–August 2020. Multivariate logistic regression analysis was carried out to determine the predictors of mortality in severe/critical COVID-19 patients.

Results Out of a total of 659 patients, 469 (71.2%) patients died. Age > 60 years, presence of hypertension, heart disease and kidney disease along with late admission (>5 days) were significant predictors of mortality in patients with severe/critical COVID-19.

Conclusions The study highlights the importance of well-timed provision of appropriate medical interventions control COVID-19-associated mortality.

Keywords corona virus disease 2019, COVID-19, Pakistan, severity, treatments

Introduction

Novel coronavirus disease 2019 (COVID-19) outbreak started from Wuhan, China in December 2019 with many cases of pneumonia of unknown causes. Within a month, the cause was identified as a new member of corona virus family, thereby named as severe acute respiratory syndrome corona virus 2.[1] The cases of COVID-19 rose drastically throughout the world within a few weeks. World Health Organization (WHO) announced it as a pandemic infectious disease on 11th of March 2020.[2]

The pathological conditions of COVID-19 infections are classified into five categories, namely; asymptomatic, mild, moderate, severe and critical, based on clinical diagnostic factors such as symptoms, oxygen saturation, respiration rates,

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X-ray and chest findings etc.[3] In severe/critical COVID-19 cases, late admissions in patients with old age, compromised immunity and comorbidities can worsen disease prognosis.[4–8]

The arsenal of available therapeutic options against COVID-19 is somewhat limited, without the ready availability of an effective vaccine to restrain its spread and a targeted antiviral agent proven to effectively eliminate the causal agent.[9] As a result, the pandemic is taking its toll on the healthcare systems worldwide.

The aim of this study was to determine the effect of timely admission to the hospital on mortality of patients with severe/critical COVID-19. Another secondary aspect of this study was to observe the efficacy of time-dependent use of corticosteroids on mortality of critical/severe COVID-19 patients.

Methods

Clinical data of 659 patients with severe/critical COVID-19 who were admitted during the period February–August 2020 to two major tertiary care hospitals in Islamabad (Pakistan Air Force Hospital and Pakistan Institute of Medical Sciences Hospital) and two major hospitals in Rawalpindi (Holy Family Hospital and Benazir Bhutto Shaheed Hospital), Pakistan were acquired retrospectively. COVID-19 diagnosis was confirmed with using polymerase chain reaction test for nasal and oropharyngeal swab samples taken at the time of admission. All cases had severe/critical cases (oxygen saturation of $<$90% on room air and respiratory rate $>$ 30/min) according to WHO COVID-19 classification criteria.[3]

The data were systematically organized and recorded using a standardized data collection form which included information on age, gender, comorbidities (diabetes, hypertension, heart diseases, chronic obstructive pulmonary disorder, kidney diseases, asthma, tuberculosis, cancer, nervous disorders, allergies, hepatitis C and anemia) and clinical symptoms (fever, cough, shortness of breath, sore throat, body ache, flu anosmia/ageusia, diarrhea, nausea/vomiting, headache and chest pain) at the time of admission, dates of onset of said symptoms, dates of admission to the hospital, basic treatments and level of care provided during stay at the hospital (i.e. admission to intensive care unit [ICU] and non-invasive or invasive ventilation) and death.

Data were collected with approval of the National Institute of Health, Pakistan. The study was approved by the ethics review board of Rawalpindi Medical University (RMU), Rawalpindi. Age was categorized into three groups, i.e. $\leq$50 year, 51–60 year and $>$ 60 years. On basis of time elapsed between onset of symptoms and admission to the hospital, patients were categorized as $\leq$ 5 (those immediately reported to the hospital within 5 days of onset of symptoms) and $>$5 (those who reported later than 5 days of onset of symptoms or late/delayed admission). Similarly, on basis of time-sensitive administration of steroids, patients were categorized into patients who immediately received steroid therapy within 3 days of admission and those that received steroid therapy later than 3 days of admission to the hospital.

The statistical analysis was conducted using IBM SPSS version 24. Categorical variables were described using frequencies and percentages. Chi-square test and Fisher's Exact tests were used to compare percentages wherever appropriate. Multivariate logistic regression analysis was carried out to determine the predictors of mortality in severe/critical COVID-19 patients. P-value of <0.05 was considered statistically significant.

Results

A total of 659 patients presented with severe or critical disease at the time of admission. Of those, 469 (71.2%) patients died and only 190 patients (28.8%) survived, who were either released into palliative care or discharged. Table 1 shows the mortality rate according demographic, clinical and relevant characteristics of 659 patients with severe or critical disease COVID-19.

Patients who died were significantly older than those who survived. About 79.7% of patients who died were older than 60 year (P-value <0.05). Moreover, a higher percentage of mortality was observed in female patients as compared with male patients (75.4% versus 69.2%, P-value = 0.108). Furthermore, a significantly higher percentage mortality was observed in patients who had hypertension (78%), heart disease (91.2%), chronic obstructive pulmonary disorder (100%), kidney disease (91.2%), hepatitis C (89.7%) and asthma (82.8%).

The mortality rate was significantly higher among patients with delayed admissions than among patients with timely admission (76% versus 66.9%, P = 0.108). No significant difference in the mortality was observed between patients who immediately received steroid therapy within 3 days of admission and those that received steroid therapy later than 3 days of admission to the hospital (P = 0.928).

Figure 1 shows the relative frequency of presenting signs and symptoms of severe/critical COVID-19 patients at the time of admission. These include fever (87.2%), cough (76.4%), shortness of breath (50.2%), sore throat (27.9%) and body aches (27.6%). Other symptoms including anosmia/ageusia and diarrhea and vomiting were not so common in severe/critical category of COVID-19 patients.

Table 1 The mortality rate according demographic, clinical and relevant characteristics of 659 patients with severe or critical disease COVID-19

Variables	*Total* *N = 659*		*Recovered* *N = 190*		*Died* *N = 469*		*P value*
	N	%	*n*	%	*n*	%	
Age (years)							<0.001
≤50	210	31.9	80	38.1	130	61.9	
51–60	173	26.3	54	31.2	119	68.8	
> 60	276	41.9	56	20.3	220	79.7	
Gender							0.108
Male	452	68.6	134	30.8	313	69.2	
Female	207	31.4	51	24.6	156	75.4	
Types of comorbidities (yes versus no)							
Diabetes	331	50.2	86	26	245	74	0.105
Hypertension	377	57.2	83	22	294	78	<0.001
Heart disease	163	24.7	28	17.2	135	82.8	<0.001
Chronic obstructive pulmonary disorder	10	1.5	0	0	10	100	0.043
Kidney disease	57	8.6	5	8.8	52	91.2	<0.001
Asthma	64	9.7	11	17.2	53	82.8	0.030
Tuberculosis	24	3.6	6	25	18	75	0.673
Cancer	8	1.2	0	0	8	100	0.070
Nervous disorders	20	3.0	2	10	18	90	0.059
Allergies	2	0.3	2	100	0	0	0.026
HCV	29	4.4	3	10.3	26	89.7	0.025
Anemia	5	0.7	0		5	100	0.153
Admission (days)							0.010
≤5	347	52.7	115	33.1	232	66.9	
>5	312	47.3	75	24	237	76	
Corticosteroid therapy (days)							0.928
≤3	321	48.7	92	28.7	229	71.3	
>3	338	51.2	98	29.0	240	71.0	

Multivariate regression analysis (Table 2) revealed that age > 60 year (OR = 1.9, 95% CI: 1.2–2.9 and $P = 0.004$), presence of comorbidities like hypertension (OR = 1.7, 95% CI: 1.1–2.4 and $P = 0.009$), heart disease (OR = 1.6, 95% CI: 1.01–2.6 and $P = 0.049$) and kidney disease (OR = 4.8, 95% CI: 1.8–12.3 and $P = 0.001$) were significantly associated with increased odds of mortality among severe/critical COVID-19 patients. Moreover, delayed admission to the hospital was a significant predictor for mortality (OR = 1.6, 95% CI: 1.1–2.3 and $P = 0.007$). However, the timing of corticosteroids therapy did not show significant association with mortality.

Discussion

In our study, the trends pertaining to the vulnerability of older patients and patients with underlying comorbidities in relation to COVID-19 associated mortality are consistent with previously reported literature, and most studies have established old age,[10] and presence of underlying comorbidities[11–14] as significant predictors of severity and mortality in COVID-19 patients. As a result, old people and patients with underlying comorbidities are touted as high-risk groups by all national and international public health regulatory forums since the beginning of the pandemic to date. Logically, controlling exposure of these high-risk groups through strict adoption of more stringent precautionary measures seems to be first and foremost strategy to not only halter the pace of this pandemic but also to reduce the overall burden of disease on hospitals.

Conversely, ensuring a timely administration of appropriate medical interventions to these high-risk patients and prioritizing their in-hospital management is also an important factor to reduce COVID-19 associated mortality.[15] There are two aspects to this strategy, timing of the therapeutic intervention

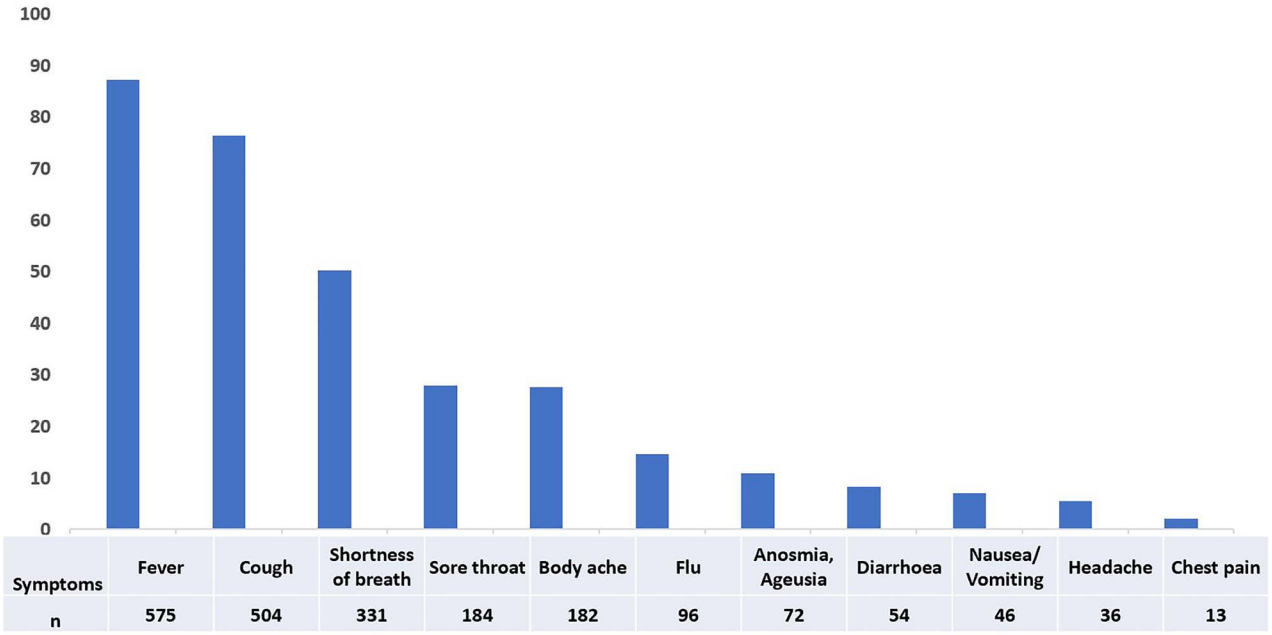

Fig. 1 The relative frequency (*n*) of presenting signs and symptoms n severe/critical COVID-19 patients at the time of admission.

Table 2 Multivariate regression analysis for factors associated with COVID-19 mortality

Covariates	*OR*	*95% CI*		*P-value*
		Lower	*Upper*	
Age (years)				
(versus ≤ 50)				
51–60	1.1	0.7	1.8	0.553
> 60	1.9	1.2	2.9	0.004
Comorbidities (yes versus no)				
Hypertension	1.7	1.1	2.4	0.009
Heart disease	1.6	1.0	2.6	0.049
Kidney disease	4.8	1.8	12.3	0.001
Admission (days)	1.6	1.1	2.3	0.007
(>5 days versus ≤ 5 days)				
Corticosteroid therapy (days)	1.0	0.7	1.4	0.978
(>3 days versus ≤ 3 days)				

Abbreviations: OR: odds ratio; CI: confidence interval.

and the efficacy of the said intervention, both of which are equally significant.

It has been consistently reported, the relative prevalence of initial presenting symptoms in mild to moderate COVID-19 patients is almost the same as patients that go on to develop severe disease [16,17]; except for shortness of breath, that has been quoted as a predictor for disease severity.[18] Moreover, hypoxemic failure results in requirement of ICU in approximately one fifth of the hospitalized COVID-19 patients.[4–7] Our data regarding relative prevalence of initial presenting symptoms in severe and critical COVID-19 patients also reported a similar trend with more severe symptoms appearing at later stages of disease after admission. It appears that while some presenting symptoms may shed a light on disease severity and poor prognosis, an immediate provision of symptomatic relief may also help in prevention of further complications. Patients with COVID-19 associated pneumonia and acute respiratory distress syndrome are more

prone to bacterial and fungal infections, especially *aspergillosis*.[19] European countries have reported that one fourth of the severe COVID-19 pneumonic patients end with fungal infections, which could be prevented with early diagnosis and treatment.[20–22] Thus, time is an important aspect, where timely administration of medical care ensures treatment efficacy. Our study further highlights the importance of this aspect. Our data suggest that if a COVID-19 patient dismisses initial symptoms combined with red flags like age, and underlying comorbidities, and delays hospital access by as many as 5 days after onset of symptoms, the likelihood of efficacy of available treatments decreases, thereby increasing the likelihood of death.

So far, the available treatment options for COVID-19 have an overall limited efficacy because most currently used therapeutic agents either provide symptomatic relief and organ support or comprise of repurposed antivirals with limited efficiency against COVID-19.[9,23] A secondary aspect of this study was to observe the effect of time-dependent use of corticosteroids on mortality of critical/severe COVID-19 patients. It should be noted that corticosteroids were a choice treatment during February–August where a major trial from UK concluded that systemic use of corticosteroids reduces mortality in severe/critical COVID-19 patients.[24] Our results indicated that steroid therapy has limited effect on reduction of COVID-19 mortality, irrespective of administration time, which is in line with a more recent analysis.[25]

An interesting consequence of this pandemic in the 21st century is the collection of evidence regarding effective therapies and development of living guidelines that update recommendations regarding their use in real-time.[23,26] A recent WHO update recommends use of corticosteroids in severe/-critical COVID-19 cases only and counter-indicates its use in patients with mild and moderate COVID-19 symptoms.[27] This further substantiates our notion about the significance of seeking time medical intervention by healthcare professionals that can ensure provision of up-to-date, immediate and effective professional healthcare.

Conclusion

Although appropriate preventive measures should be undertaken by high-risk groups, proper awareness regarding symptoms and the significance of seeking timely medical care ahead of time are important factors that ensure treatment efficiency and may reduce mortality in severe/critical COVID-19 patients. Limited efficacy of available treatments, however, might contribute to an increase in-hospital admissions, long hospital stays and increased in-hospital deaths, which inadvertently increases the burden of disease on hospitals. This alludes to the importance of development of alternate strategies like outpatient evaluations and remote which can simultaneously ensure appropriate timely medical support and relieve burden of disease in hospitals.

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Conflict of Interest

The authors declare no conflict of interest.

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