



Predictors of mortality among hospitalized COVID-19 patients

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ARTICLE INFO

Article No.: 122122106

Type: Research

Full Text: [PDF](#), [HTML](#), [PHP](#), [EPUB](#)

Accepted: 22/12/2022

Published: 28/12/2022

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Keywords: Admitted, COVID-19, mortality, associated factors.

ABSTRACT

Background: On 14 November 2022, 6,588,850 deaths from COVID-19 reported to WHO. Older age as well as pre-existing conditions, such as cardiovascular disease, chronic kidney disease, chronic lung diseases, diabetes mellitus, and hypertension predispose patients to increased risk death.

Methods: This study is a retrospective case-control one that was conducted by reviewing records of all admitted COVID-19 patients in Jaber hospital in Kuwait during the period from February till May 2019. Analysis was initially carried on a series of univariate comparisons, followed by multiple logistic regression analysis.

Objectives: This study aimed at highlighting some factors that could be associated with mortality of COVID-19 in admitted cases during the first wave of the disease.

Results: After adjustment for the confounding effects, admitted COVID-19, older age seemed to be at higher risk of death, as patient in the age group 40-49, 50-59 and ≥ 60 years old were more prone to death as compared to those in the age group < 40 years (OR = 7.8, CIs: 3.2 – 27.0), (OR = 10.5, CIs: 4.8 – 36.5) and (OR = 18.3, CIs: 9.2 – 30.8) respectively. Patients with hypertension were 3.9 folds liable for death during hospital stay (CIs: 2.5 – 5.9), and patients with cardiac disease were 3.7 folds prone for death (CIs: 1.9 – 7.8). Also, diabetic patients and those with pulmonary disease were significantly more prone to die during their hospital stay (OR = 6.1, CIs: 2.8 – 8.2) and (OR = 5.0, CIs: 1.7 – 8.8) respectively. Patients with low level of blood oxygen on admission were 7.6 folds at risk of dying (CIs: 3.9 – 12.7) and those who needed ICU admission were 41 folds more liable to die during hospital stay (CIs: 15.1 – 69.2).

Conclusions: Among the main predictors of mortality among admitted COVID-19 cases are age, comorbidities, SpO2 percentage and lymphocytic count in addition to admission to the intensive care unit.

INTRODUCTION:

On 11 March 2020, the World Health Organization (WHO) declared the novel coronavirus disease 2019 (COVID-19) as a pandemic. (WHO, 2020) COVID-19 is characterized by poor outcomes and mortality, especially among older patients. (Lithandwe et al., 2020). The outbreak of COVID-19 pandemic is not only a challenge for national health systems, but it has equally forbidden the economic and social life of people across the globe. (Gacche et al., 2021) As accessed on 10th January 2021, according to WHO, over 106.32 million people are suffering from COVID-19 with a toll of over 2.32 million COVID-19 related deaths. Globally, on 14 November 2022, there have been 631,935,687 confirmed cases of COVID-19, including 6,588,850 deaths, reported to WHO. (WHO, 2022)

Several studies analyzed the factors affecting morbidity and mortality in hospitalized patients with COVID. (Li LQ et al., 2020; Alqahtani et al., 2020; Huang, 2020; Li X et al., 2020; Tian et al., 2020; Liu Y et al., 2020; Shi et al., 2020; Bhatraju et al., 2020; Zhang L et al., 2020) In the early phase of clinical observation, respiratory failure was attributed as a major cause of morbidity and mortality of COVID-19 patients. (Gacche et al., 2021) However, the upcoming clinical and epidemiological data links it with patients having pre-existing history of hypertension, chronic obstructive pulmonary disease, diabetes, coronary heart disease, and kidney comorbidities have worse clinical outcomes when infected with SARS-CoV-2. (Lippi et al., 2020; Lippi and Henry, 2020; Xu et al., 2020; Mehra et al., 2020; Cheng et al., 2020) Pre-existing conditions, such as cardiovascular disease, chronic kidney disease, chronic lung diseases (particularly COPD), diabetes mellitus, hypertension, immunosuppression, obesity, and sickle cell disease, predispose patients to an unfavorable clinical course and increased risk of intubation and death. (Zhout et al., 2020; Huang C et al., 2020; Cecconi et al., 2020; Zhu et al., 2020; Price et al., 2020; Chen T et al., 2020; Huang S et al., 2020; Guo et al., 2020) In general, the most commonly observed comorbidities in COVID-19 patients are hypertension followed by diabetes, chronic cardiovascular disorders, cerebrovascular diseases, COPD, and chronic kidney dysfunction. (Zhou et al, 2020)

Certain demographic factors reported in the literature are associated with a higher rate of a severe clinical course of COVID-19. (Mani et al., 2020; Cecconi, et al., 2020; Chen N et al., 2020) Among these, older age is a major predictor of mortality and it is thus considered a key factor in the proposed clinical severity and mortality of Coronavirus disease. (Cecconi, et al., 2020) China Center for Disease Control and Prevention reported that the older age and comorbidities were all associated with higher risk of death in COVID-19. (Wu and McGoogan, 2020; Imam et al., 2020; Ciceri et al., 2020; Galloway et al., 2020)

Data also suggest that male sex is a variable that is independently associated with COVID-19 severity. (Palaodimos et al., 2020; Li X et al., 2020)

Severe COVID-19 is characterized by Acute Respiratory Distress Syndrome (ARDS), sepsis, multi-system organ failure, hyperinflammation, neurological and other extra-pulmonary manifestations, and thromboembolic disease. (Grasselli et al., 2020; Guan et al., 2020; Zhout et al., 2020; Yang X et al., 2020). In a previous study, the author found that during hospitalization, 24.8% of patients developed renal failure, 60.1% patients developed respiratory failure, 9.7% suffered heart failure, 16.7% suffered sepsis and 23.5% developed systemic inflammatory response syndrome. Almost 80% required oxygen during admission and 6.4% used mechanical ventilation. (Becerra-Munoz, 2021)

Some other factors that could be associated with severity and mortality of COVID-19 were mentioned in previous studies. A strong association between hypoxemia and worse clinical outcomes has been reported. (Duan et al., 2020; Xie et al., 2020) Also, a recent meta-analysis identified statistically significant reductions in total lymphocytes count. (Huang W et al, 2020)

Identification of potential risk factors that predict the disease course may be of great utility for healthcare professionals to efficiently triage patients, personalize treatment, monitor clinical progress, and allocate proper resources at all levels of care to mitigate morbidity and mortality. This study aimed at highlighting some factors that could be associated with mortality of COVID-19 in admitted cases during the first wave of the disease.

SUBJECTS AND METHODS:

Setting:

This study is a part of a larger one that was conducted in Jaber Al-Ahmed hospital. The time interval of the study was set as four months from April to July 2021. The details of the study design, sampling and research tool were described elsewhere (Al-Zuabi et al., 2022) Studied patients were classified into 2 groups: cases (those who were died) and control (who were discharged alive). Research tool included personal characteristics, associated co-morbid conditions, presenting symptoms, investigations and vital signs on admission, COVI-19 complications, as well as outcome parameters. The study was approved by the Ethics Committee of the Kuwaiti Ministry of Health. The permission of the Deputy Ministry of Health in Kuwait as well as head of Jaber hospital were obtained.

Statistical analysis:

Analysis was initially carried out based on a series of univariate comparisons. In order to control

simultaneously for possible confounding effect of the variables, multiple logistic regression was used for the final analysis. In the univariate analysis Chi-square test was used to detect the association between mortality and explanatory variables. In multiple logistic regression analysis, the association between exposure and outcome was expressed in terms of odds ratio (OR) together with their 95% confidence intervals (95% CIs).

All the explanatory variables included in the logistic model were categorized into two or more levels (R = reference category): gender: male^R, female; age (years): < 40^R, 40 – 49, 50 – 59, ≥ 60; nationality: Kuwaiti^R, non-Kuwaiti; Governorate: Capital^R, Hawally, Farwaniya, Ahmadi, Jahar, Mubarak; smoking: no^R, yes; history of hypertension: no^R, yes; history of cardiovascular disease: no^R, yes; history of diabetes mellitus: no^R, yes; history of pulmonary disease: no^R, yes; ApO2 level: normal^R, low; lymphocytic count: normal^R, low, high; FBS: normal^R, prediabetic, diabetic; no^R, yes; ICU admission: no^R, yes; days of hospital stay: <10^R, 10-14, 15-19, ≥20. Analysis was performed using SPSS package 22.

RESULTS:

Reviewing the medical records of the cases admitted to the selected hospital during the defined period resulted in inclusion of 1482 positive cases for COVID-19. One thousand and four hundred twenty five cases were discharged alive (96.2%) and 57 (3.8%) were died and subjected to the final analysis.

Table 1 describes the personal characteristics of the included patients according to their outcome on discharge. The mean age of the control group (42.8±12.8) was insignificantly lower than that of the case group (57.0±13.6), $p < 0.001$.

Table 2 shows the frequency of co-morbid chronic diseases among the studied patients. The proportions of hypertension, cardiovascular, diabetes mellitus, respiratory diseases were significantly higher in died than alive cases ($\chi^2 = 40.98$, $P > 0.001$), ($\chi^2 =$

14.94, $P < 0.001$), ($\chi^2 = 31.82$, $P < 0.001$), and ($\chi^2 = 1.22$, $P < 0.001$) respectively.

As shown in table 3, higher proportion of died cases (54.4%) complained from general symptoms than alive ones (32.9%) significantly ($\chi^2 = 11.31$, $P = 0.001$). Also, the proportion of respiratory symptoms was significantly higher among died than alive cases (71.9% versus 42.2%, $p < 0.001$). Low blood oxygen level on admission was significantly more encountered among cases than controls (26.3% versus 4.3%, $p = 0.001$). Also, abnormal lymphocytic count (low or high) was significantly more encountered among died cases, $p < 0.001$. the percentage of diabetic patients was significantly higher among cases than controls (71.9% versus 25.8%, $p < 0.001$)

After adjustment for the confounding effects between variables, table 4 illustrated variables that retained as significant determinants for the outcome of interest (death). Older age seemed to be at higher risk of death among admitted COVID-19 cases as patient in the age group 40-49, 50-59 and ≥ 60 years old were more prone to death as compared to those in the age group < 40 years (OR = 7.8, CIs: 3.2 – 27.0), (OR = 10.5, CIs: 4.8 – 36.5) and (OR = 18.3, CIs: 9.2 – 30.8) respectively.

Regarding chronic co-morbid conditions, patients with hypertension were 3.9 folds liable for death during hospital stay (CIs: 2.5 – 5.9), patients with cardiac disease were 3.7 folds prone for death (CIs: 1.9 – 7.8). Also, diabetic patients and those with pulmonary disease were significantly more liable to die during their hospital stay (OR = 6.1, CIs: 2.8 – 8.2) and (OR = 5.0, CIs: 1.7 – 8.8) respectively.

Those patients with low blood oxygen level on admission were 7.6 folds at risk of dying (CIs: 3.9 – 12.7). Patients who were in need of ICU admission were 41 folds more liable to die during hospital stay (CIs: 15.1 – 69.2). Lastly, it was found that hospital stay ≥ 10 days was significantly associate with higher probability of death as hoospital stay: 10-14 days (OR = 3.6, CIs: 1.9 – 7.2), 15-19 days (OR = 2.7, CIs: 1.5 – 7.3), and ≥ 20 days (OR = 4.8, CIs: 1.8 – 9.9).

Table (1): Distribution of hospitalized COVID-19 patients according to personal characteristics and outcome on discharge

Personal characteristics	Alive (n=1425)		Dead (n=57)		Test of significance (p)
	No.	%	No.	%	
Gender					
Male	1099	77.1	49	89.5	$\chi^2=2.45$
Female	326	22.9	8	10.5	P=0.12
Age (years)					
<40	660	46.3	3	5.3	$\chi^2=53.07$
40-49	347	24.4	17	29.8	P<0.001
50-59	245	17.2	15	26.3	
≥60	173	12.1	22	38.3	
Mean ± SD	42.8 ± 12.8		57.0±13.6		t = 8.20
Min - Max	19 – 85		22 - 94		P < 0.001
Nationality:					
Kuwaiti	349	24.5	9	15.8	$\chi^2=2.27$
Non-Kuwaiti	1076	75.5	48	84.2	P = 0.13
Governorate					
Capital	350	24.6	13	22.8	$\chi^2=1.97$
Hawalli	288	20.2	11	19.3	P = 0.85
Farwaniyah	426	29.9	21	36.8	
Ahmadi	229	16.1	9	15.8	
Jahra	59	4.1	1	1.8	
Mubarak Alkabeer	73	5.1	2	3.5	
BMI:*					
Under-weight / Normal	179	33.8	2	16.7	$\chi^2=3.13$
Over-weight	219	41.4	8	66.7	P = 0.21
Obese	131	25.7	2	16.6	
Mean ± SD	25.5 ± 5.3		267.6 ± 3.9		t = 0.09
Min - Max	16.18 – 59.86		22.78 – 38.052		p = 0.93
Smoking:					
No	1368	96.0	55	96.5	Fisher's Exact
Yes	57	4.0	2	3.5	P = 1.00

*: missing 739 males and 202 females

Table (2): Distribution of hospitalized COVID-19 patients according to chronic co-morbid diseases and outcome on discharge

Co-morbid diseases	Alive (n=1425)		Dead (n=57)		Test of significance (p)
	No.	%	No.	%	
Hypertension					
No	1179	82.7	28	49.1	$\chi^2=40.98$
Yes	246	17.3	29	50.9	P<0.001
Cardiovascular					
No	1361	95.5	48	84.2	$\chi^2=14.94$
Yes	64	4.5	9	15.8	P<0.001
Diabetes mellitus					
No	1204	84.5	32	56.1	$\chi^2=31.82$
Yes	221	15.5	25	43.9	P<0.001
Pulmonary diseases					
No	1373	96.4	49	86.0	$\chi^2=15.22$
Yes	52	3.6	8	14.0	P<0.001

Table (3): Distribution of hospitalized COVID-19 patients according to the presenting symptoms and investigations on admission and outcome on discharge

Symptoms & Investigation	Alive (n=1425)		Dead (n=57)		Test of significance (p)
	No.	%	No.	%	
General symptoms					
No	956	67.1	26	45.6	$\chi^2=11.31$
Yes	469	32.9	31	54.4	P=0.001
Respiratory symptoms					
No	823	57.8	16	28.1	$\chi^2=19.66$
Yes	602	42.2	41	71.9	P<0.001
Gastro-intestinal symptoms					
No	1334	93.6	51	89.5	$\chi^2=1.54$
Yes	91	6.4	6	10.5	P=0.22
SpO2					
Normal	1364	95.7	42	73.7	$\chi^2=54.70$
Low	61	4.3	15	26.3	P<0.001
Lymphocytic count					
Normal	1240	87.0	27	47.4	$\chi^2=70.54$
Low	172	12.1	27	47.4	P<0.001
High	13	0.9	3	5.3	
FBS					
Normal	656	46.0	4	7.0	$\chi^2=62.19$
Pre-diabetic	402	28.2	12	21.1	P<0.001
Diabetic	367	25.8	41	71.9	
Duration of Hospital stay (days)					
< 10	751	52.7	11	19.3	$\chi^2=26.38$
10-14	194	13.6	13	22.8	P<0.001
15-19	206	14.5	11	19.3	
≥20	274	19.2	22	38.6	
ICU admission					
No	1355	95.1	4	7.0	$\chi^2=558$
Yes	70	4.9	53	93.0	P<0.001

Table (4): Factors associated with mortality of admitted COVID-19 patients.

Variables	Odds Ratio	95% CI
Age (years)		
< 40 ^R	1	
40 - 49	7.8	(3.2 – 27.0)
50 - 59	10.5	(4.8 – 36.5)
≥ 60	18.3	(9.2 – 39.8)
Co-morbidity		
Hypertension		
No ^R	1	
Yes	3.9	(2.5 – 5.9)
Cardio diseases:		
No ^R	1	
Yes	3.7.0	(1.9 – 7.8)
Diabetes mellitus:		
No ^R	1	
Yes	6.1	(2.8 – 8.2)
Pulmonary disease:		
No ^R	1	
Yes	5.0	(1.7 – 8.8)
SpO2:		
Normal ^R	1	
Low	7.6	(3.9 – 12.7)
Duration of hospital stay (days)		
<10 ^R	1	
10-14	3.6	(1.9 – 7.2)
15-19	2.7	(1.5 – 7.3)
>20	4.8	(1.8 – 9.9)
ICU admission:		
No ^R	1	
Yes	40.9	(15.1 – 69.2)

^R = Reference category, OR = Odds ratio, CI = Confidence interval

DISCUSSION:

The large number of COVID19-infected patients admitted to hospitals necessitate clear understanding of demographic, clinical and laboratory findings that may lead to high rates of mortality. (Marin et al., 2021) It was demonstrated that primary personal characteristics rather than viral characteristics are playing a key role in determining severity of COVID-19 disease. (Zhang X et al., 2020) In order to enable health care workers to properly manage cases, describe the suitable therapeutic regimens as well as to properly allocate resources; it is essential to determine the potential risk factors that are associated with bad prognosis and mortality.

Many studies dealt with the factors affecting mortality among hospitalized COVID-19 patients. (Li LQ et al., 2020; Huang I et al., 2002; Liu K et al., 2020) Old age was demonstrated as key demographic predictor of both severe morbidity and mortality. (Cecconi et al., 2020; Imam et al., 2020; Ciceri et al., 2020; Galloway et

al., 2020) The current study revealed that there is and increasing odds of mortality with increase of age (odds ratio = 7.8, 10.5 and 18.3 for each decade compared with those less than 40 years). Old age was demonstrated to be a poor prognostic predictor among hospitalized COVID-19 cases. (Grasselli et al., 2020; Zhou et al., 2020; Huang et al., 2020; Li X et al, 2020) Actually, older age has been recognized as a predicting risk factors for both severe morbidity and mortality since the early start of COVID-19 epidemic. (Huang et al., 2020; Guang C et al., 2020; Zhou et al., 2020) Several explanations were provided for the higher mortality among the elderly COVID-19 patients; one study revealed that those older than 65 years suffered from higher rates of comorbidities, abnormal laboratory findings and multiple organ failure than the younger patients (Chen T et al., 2020) while another retrospective study in Italy revealed a lower partial pressure of oxygen to fraction of inspired oxygen ratio (PaO₂/FiO₂) among the older COVID-19 patients

compared with the younger patients. (Grasselli et al., 2020)

The current study revealed that deaths were more likely encountered among males than females with a case fatality of 4.3% and 2.4% respectively, however this difference is not statistically significant. It was postulated that females are less prone to develop a severe form of COVID-19 but, they have the same risk of mortality as males if they already developed the disease (Bellan et al., 2020). However, other studies, in contradiction to the current study, revealed that being a male is a significant risk predictor of severe morbidity of COVID-19. (Palaodimos et al., 202; Li et al., 2020)

Several comorbidities that the COVID-19 patients are suffering from may be associated with severe forms of the disease or even mortality. (Zhou et al., 2020; Mehra et al., 2020; Liang et al., 2020; Cheng et al., 2020). The current study revealed that the most common comorbidities related to death of the hospitalized COVID-19 patients were high blood pressure (50.9%, OR = 3.9), Diabetes mellitus (43.9%, OR = 6.1) followed by Other cardiovascular disorders (15.8%, OR = 3.7) and pulmonary diseases (14.0%, OR = 5.0). These findings are similar to and confirm other clinical universal findings that identified hypertension as the most commonly comorbidity associated with COVID-19 mortality. (Lippi G et al., 2020; Zhou et al., 2020; Aggarwal et al., 2020) Zhou and his colleagues, in China, revealed that Hypertension followed by diabetes were the most common associated comorbidities with COVID-19 deaths. (Zhou et al., 2020) In a pooled analysis study, the odds of death of those suffering from hypertension was 2.5 folds those not suffering from hypertension; a figure which is lower than that revealed by this study (3.9). (Lippi G et al., 2020) Also, the American College of Cardiology pointed out that the fatality rates were highest for cardiovascular disease (10.5%) compared with diabetes (7.3%), and hypertension (6.0%). (Mullen et al., 2020) The results of the current study are slightly higher than those of the previous study with a fatality rate of 12.3% for cardiovascular diseases, 10.5% for hypertension and 10.1% for diabetes mellitus. This difference may be attributed to the level of medical care or genetic characteristics of the prevalent virus strain of COVID-19 disease.

Previous studies revealed that lymphopenia was not only more commonly encountered among COVID-19 patients (Liu Y et al., 2020; Tjendra et al., 2020) but also it was associated with poor outcome. (Guan et al., 2020; Sun et al., 2020) The current study revealed that low lymphocyte counts at hospital admission was significantly associated with higher mortality among COVID-19 cases. This finding confirms that revealed by other previous studies. (Mendes et al., 2020; Guan G et al., 2020; Huang W et al., 2020; Zheng et al., 2020; Ma et al., 2020). The uncontrolled innate immune responses and impaired adaptive immune signaling that are linked to lymphopenia might contribute to the occurrence of local and systemic

tissue damage that may explain the higher deaths and bad prognosis of hospitalized COVID-19 patients suffering from low lymphocytic count. (Tay et al., 2020; Qin et al., 2020; Cao, 2020)

A strong association between hypoxemia and bad prognosis has been revealed. (Duan et al., 2020; Xie et al., 2020) The current study revealed that hospitalized COVID-19 patients with low SpO₂ were 7.6 times more liable to death than those with normal SpO₂. One study showed that SpO₂ more than 90.5% could predict survival among COVID-19 patients. (Xie et al., 2020) This may explain the significantly high rate of COVID-19 patients admission to the intensive care unit. As one of the main criteria for intensive care unit admission is low SpO₂ percentage in addition to other factors that may immediately the life of such cases.

The main limitations of the current study is being hospital based and depending mainly on secondary data (records of hospitalized patients). Also the criteria for hospital or intensive care units may differ among countries, however, the large number of recruited cases and a selection of the only specialized hospital to deal with COVID-19 cases from all districts of Kuwait can provide both power and advantage for carrying out this study.

CONCLUSIONS:

To maintain and enhance the health of hospitalized COVID-19 patients it is essential to identify the risk factors that might contribute to death including age, comorbidities, SpO₂ percentage and lymphocytic count in addition to admission to the intensive care unit.

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