Risk factors for mortality among COVID-19 patients

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ABSTRACT

Aims: COVID-19 is a current global pandemic. However, comprehensive global data analyses for its mortality risk factors are lacking. The current investigation aimed to assess the predictors of death among COVID-19 patients from worldwide open access data.

Methods: A total of 828 confirmed cases of COVID-19 with definite outcomes were retrospectively identified from open access individual-level worldwide data. Univariate followed by multivariable regression analysis were used to evaluate the association between potential risk factors and mortality.

Results: Majority of the patients were males 59.1% located in Asia 69.3%. Based on the data, older age (adjusted odds ratio (aOR), 1.079; 95% confidence intervals (95% CI), 1.064–1.095 per year increase), males (aOR, 1.607; 95% CI, 1.002–2.576), patients with hypertension (aOR, 3.576; 95% CI, 1.694–7.548), diabetes mellitus (aOR, 12.234; 95% CI, 4.126–36.272), and patients located in America (aOR, 7.441; 95% CI, 3.546–15.617) were identified as the risk factors of mortality among COVID-19 patients.

Conclusions: Males, advanced age, hypertension patients, diabetes mellitus patients, and patients located in America were the independent risk factors of death among COVID-19 patients. Extra attention is required to be given to these factors and additional studies on the underlying mechanisms of these effects.

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1. Introduction

An outbreak of viral pneumonia with an unidentified etiology was announced in Wuhan city, China, on 12 December 2019 [1,2]. Further researches indicated the presence of a novel coronavirus which had been quickly isolated, and its genome had been sequenced [3]. The World Health Organization (WHO) named this virus as the 2019 novel coronavirus (2019-nCoV) [4] and subsequently it was named Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) by the *Coronaviridae* Study Group (CSG) of the International Committee on Taxonomy of Viruses [5]. Officially, COVID-19 became the name of the disease that is caused by the aforementioned virus [5].

SARS-COV-2 started from a local seafood market in Wuhan of a probable bat origin since it is 96% genomically similar to a bat coronavirus (BatCoV RaTG13) [6,7] and the infection became hard to control or prevent ever since Chinese health authorities declared a possibility of person to person transmission even if subjects were asymptomatic [6]. On 11 March 2020, WHO announced COVID-19 as global Pandemic [8] that appear to be disseminating at an extreme rate, as of April 21st, 2020, at least 2 314 621 cases confirmed, 157 847 cases death [9].

COVID-19 symptoms differ among patients and may include fever, cough, breathing difficulties, organ failures, and in its severe levels, COVID-19 may lead to death and thus threaten the whole society [6]. Older age, increased D-Dimer, and higher Sequential Organ Failure Assessment score were identified as the risk factors for mortality of COVID-19 in one investigation in China [2]. The aim of this study is to evaluate risk factors for COVID-19 mortality in worldwide open-access data that offers a wider range of population data.

2. Subjects, materials and methods

2.1. Study design

The cross-sectional study design was implemented to extract all COVID-19 positive patients who had a definite outcome from the open-access individual-level data reported by Xu, et al. [10] on April 21st, 2020. These data were compiled from national, provincial, municipal health reports, and online reports. A live version of the data record in CSV format can be downloaded from (https://github.com/beoutbreakprepared/nCoV2019) or from Google Drive: https://docs.google.com/spreadsheets/d/1itaohdPiAeniCXNlntNztZ_oRvjh0Hs-GuJXUJWET008/edit#gid=0.

2.2. Data collection

Demographic data about the age and sex of patients/cases, as well as chronic comorbidities and key dates such as date of symptoms onset, hospital admission, COVID-19 infection diagnosis confirmation, and discharge or death, were collected. Travel history and dates, as well as geographical information, were also available. Mortality was defined as those patients with an outcome labeled as "dead", "died", "death", or "deceased", while survival was defined as those patients with an outcome labeled as "alive", "discharge", "discharged", "discharged from hospital", "not hospitalized", "recovered", "recovering from home", "released from quarantine", "stable", or "stable condition". Other labels implying critical, severe, or under treatment cases were excluded from the analysis. Risk factors of mortality, including non-modifiable sex, age, geographic location, and modifiable chronic diseases, were evaluated among COVID-19 patients.

2.3. Statistical analysis

Multivariable logistic regression was used to evaluate risk factors of mortality among COVID-19 patients using SPSS version 24.0 (SPSS Inc., Chicago, III, USA). Univariate analysis of categorical variables was performed using the Chi-square test, while an independent sample t-test/Mann Whitney U test was used for continuous data. Multivariable analysis using logistic regression was performed for the risk factors found to be significant in the univariate analysis. Odds ratio (OR) with 95% confidence interval (CI) were used to report the association between mortality and exposure to the risk factors. The pattern of independent variables' missing data was analyzed to minimize the bias caused by missing values.

Multiple imputations method was used to handle variables with missing data of more than 5%. Five imputations were performed and combined through Rubin's rules.

3. Results

3.1. Patients' demographics and clinical data

Demographic and clinical characteristics of the patients can be found in Table 1. Data of 1456 patients including outcomes were available; of them, 828 patients from 32 different countries were considered to have definite outcomes and thus were extracted and included in the analysis with a mean ± SD age of 49.4 ± 20.9; of them, 489 were males, and 128 had chronic diseases. Patients were most commonly located in Asia 69.3%, and the most common chronic disease was hypertension 10.9%. From the available data, 219 (26.4%) of the patient had died from the COVID-19. Multiple imputations method was successfully applied to 20% of the missing age and 18.5% of the missing sex data, respectively.

3.2. Predictors of mortality among COVID-19 patients

The results of the multivariable analysis are summarized in Table 2. Older age (adjusted odds ratio (aOR), 1.079; 95% confidence intervals (95% CI), 1.064–1.095 per year increase), males (aOR, 1.607; 95% CI, 1.002–2.576), hypertension patients (aOR, 3.576; 95% CI, 1.694–7.548), and diabetes mellitus patients (DM) (aOR, 12.234; 95% CI, 4.126–36.272) were identified as the risk factors of mortality among COVID-19 patients. Furthermore, patients located in America (aOR, 7.441; 95% CI, 3.546–15.617) had a higher risk of COVID-19 mortality as compared to those located in Asia. Chronic lung diseases, chronic kidney disease, and cardiovascular diseases were found to be associated with COVID-19 mortality. However, they were insignificant factors in the multivariable analysis.

Table 1 – Demographic and clinical characteristics of COVID-19 patients (N = 828).

Sign/Symptom	N (%)
Age	49.4 ± 20.9[*]
Sex	
Female	339 (40.9)
Male	489 (59.1)
Geographic location	
Asia	574 (69.3)
Africa	139 (16.8)
America	60 (7.2)
Europe	31 (3.7)
Australia	24 (2.9)
Chronic diseases	128 (15.5)
Hypertension	90 (10.9)
Diabetes mellitus	62 (7.5)
Chronic lung diseases	20 (2.4)
Chronic kidney disease	16 (1.9)
Cardiovascular diseases	23 (2.8)
Mortality	219 (26.4)

[*] Mean ± SD.

Table 2 – Risk factors for mortality among COVID-19 patients (N = 828).

Variable	Univariate analysis		Multivariable analysis		
	Mortality, n (%)	P-value	aOR	95% CI	P-value
Age	−26.5[*]	<0.001	1.079	1.064–1.095	<0.001
Sex		0.066			
Female	78 (23.0)			Reference	
Male	141 (28.8)		1.607	1.002–2.576	0.049
Geographic location		<0.001			
Asia	148 (25.8)			Reference	
Africa	20 (14.4)		1.207	0.637–2.286	0.564
America	42 (70.0)		7.441	3.546–15.617	<0.001
Europe	7 (22.6)		1.752	0.540–5.685	0.351
Australia	2 (8.3)		0.463	0.083–2.592	0.381
Chronic diseases					
Hypertension	75 (83.3)	<0.001	3.576	1.694–7.548	0.001
Diabetes mellitus	57 (91.9)	<0.001	12.234	4.126–36.272	<0.001
Chronic lung diseases	16 (80.0)	<0.001	4.205	0.919–19.249	0.064
Chronic kidney disease	16 (100)	<0.001	–	–	0.998
Cardiovascular diseases	20 (87.0)	<0.001		Removed	

Classification table 87.4% correctly classified using backward logistic regression method, Constant = −6.294. Area under the receiver operating characteristic (ROC) curve [95% CI] = 0.915 [0.893–0.938].
aOR, Adjusted odds ratio; 95% CI, 95% Confidence intervals.
[*] Mean difference of the student *t*-test.

4. Discussion

In this study, predictors of mortality among COVID-19 from worldwide open access data were evaluated. Age appears to be a crucial factor of COVID-19 outcome. It was stated in previous studies that deceased patients have a median age of 68 years old and were significantly older than recovered patients [11]. Furthermore, 80% of deaths associated with COVID-19 were found to be among adults aged ≥ 65 years. Thus, advanced age was found to be a risk factor for COVID-19 mortality [2,12], which was consistent with the current investigation. Similar results were also demonstrated in SARS and MERS infected patients [13,14]. A higher peak viral load was found among older age COVID-19 patients. However, the difference in the median viral load between severe and mild cases was not significant [15], whereas a high initial viral load was found to be associated with death in SARS-CoV infected patients [16]. Advanced age patients have a probably weaker immune response; therefore, they are more susceptible to the development of acute respiratory distress syndrome ARDS and mortality [17].

It was indicated in a previous study on macaques injected with SARS-CoV that aged macaques developed acute lung injury. Genomic analyses stated that aged macaques have excess differential expression of genes related to inflammation in addition to the higher host response to virus infection than young adult macaques [2,18]. Elderly patients were found to experience age-dependent defects in T and B lymphocytes function in addition to a noticeable decline in cell-mediated immune function and reduced humoral immune function. The increased production of type 2 cytokines could weaken the control of viral replication and cause more prolonged pro-inflammatory responses and eventually, a poor outcome [2,19].

Consistent with the current findings, it has been reported that males had higher mortality than females [20–22]. Males were found to be less prevalent in the recovery group as compared to the deceased group [2,11]. Higher mortality was attributed to a higher rate of chronic comorbidities among males, such as cardiovascular diseases, hypertension, and lung diseases, as well as a higher rate of smoking [20]. Other studies have explained the sex difference in COVID-19 mortality by higher expression of ACE2 receptor which was found in Asian males [23]. Human coronaviruses SARS-CoV and SARS-CoV-2 bind to ACE2 receptors in the host pneumocytes [24].

To our knowledge, this the first study to investigate differences in COVID-19 mortality based on geographical location. Worldwide geographical discrepancies in COVID-19 incidence and mortality were observed, such as lower incidence in Africa [25,26], which could be attributed to many reasons including behavioral, cultural, and social differences such as poor socioeconomic status and health-seeking and cohabitation practices, as well as variations in attitudes, immune profiles, risk of infection and comorbidities [27].

It was reported that patients with chronic comorbidities were associated with a severe COVID-19 condition [28,29]. Particularly, those with previous cardiovascular, metabolic diseases [29]. More severe disease, acute respiratory distress syndrome, and increased mortality were associated with DM. This might be attributed to an impaired innate immunity which is the first line of defense against SARS-CoV-2 [30], chronic inflammation or increased coagulation activity among DM patients [31]. It has been shown that diabetes and hypertension treatments with angiotensin-converting enzyme inhibitors (ACE inhibitors) and angiotensin II type I receptor blockers (ARBs) increase ACE2 expression which consequently raises the risk of developing severe and fatal

COVID-19 [24]. On the other hand, ACE inhibitors and ARBs were reported to decrease mortality and endotracheal intubation in patients with viral pneumonia since they reduce inflammatory response by decreasing cytokines [31]. However, there was no evidence that ACE inhibitors or ARBs affected the mortality risk of COVID-19 combined with CVD [31,32].

It was demonstrated that COVID-19 patients with a history of cardiovascular diseases (CVD) [33] or chronic obstructive pulmonary disease (COPD) [34] had higher odds of mortality. This was inconsistent with the current results, possibly; due to the low number of cases with chronic lung diseases or CVD.

This study had limitations due to its retrospective nature and due to the open-access data nature itself despite the efforts that have been made to validate it. Furthermore, CVD and chronic lung diseases were reported in a low number of patients. Other clinical and laboratory data to assess patient disease status were unavailable. Smoking status and other socioeconomic status were also lacking. The reported mortality might not reflect the actual percentage due to the exclusion of patients still on treatment and variable availability of patient outcomes worldwide as well as the unequal distribution of reported cases.

In the current study, risk factors for COVID-19 mortality among a large sample of patients worldwide were evaluated. Male, advanced age, patients with hypertension, diabetes mellitus patients, and patients located in America were independent risk factors of death among COVID-19 patients. Extra attention should be given to these factors, and further evaluations should be performed to investigate the underlying mechanisms of these effects.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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