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Coronavirus Pandemic

Health related factors contributing to COVID-19 fatality rates in various communities across the world

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Abstract

Introduction: Factors such as comorbidity, age and gender distribution are mostly related to hospitalization, numbers requiring intensive care and case fatality rate. In this review, the fatality rate of coronavirus disease 2019 (COVID-19) in different population health background according to comorbidity, age, gender distribution, and laboratory prognosis for COVID-19.

Methodology: The current review was based on the data from copious studies that had homogeneity in relation to the review's objectives. It included the newest studies from December 2019 to September 2020. The epidemiological reasons for the high morbidity and mortality rates among COVID-19 patients were analyzed in different countries.

Results: The highest comorbidity prevalence of COVID-19 was recorded in the United States of America (USA) (93.9%) and Italy (68%). Among population health background factors, comorbidity was the most common cause of COVID-19 fatality in the USA. The mean age of the most COVID-19 fatalities was more than 60 years old. Most of the studies show that 60% of COVID-19 patients were male. The fatality rates for the age group of 80-89 years-old in Korea, China, and Italy were 8.7 %, 14.7 %, and 18.8 % respectively. Lymphocytopenia has been observed in 91% of COVID-19 death cases. C - reactive protein had increased in 40-60% of COVID-19 patients.

Conclusions: Many factors contribute to COVID-19 severity and fatality rates. Comorbidity, age, and gender were the main reasons for the Case Fatality Rate. This review recommends to follow preventive measures for overcoming the challenges faced during this emerging pandemic disease.

Key words: COVID-19; case fatality rate; epidemiology; immunology; comorbidity.

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Introduction

Coronavirus disease 2019 (COVID-19) is a pandemic disease that arose as an outbreak in Wuhan city of China in December 2019. This pandemic outbreak exponentially cause deterioration of the economic, medical and public health infrastructure of countries around the world [1]. This novel coronavirus (2019-nCoV) possibly originated from Bat-SARS-like-coronaviruses or/and coronavirus isolated from Pangolin after the adaptation and evolution in human hosts [2]. The epidemiological characteristics of the disease have assisted in the controlling and prevention of this pandemic disease. Furthermore, different health systems, community health and demographic conditions have responded to the disease impacts and fatalities.

Several measures have been used to reduce the spread of the disease and reduce fatality rate. The most important control measures were including border control, case identification, and extensive investigation of COVID-19, quarantine of suspicious cases, isolation, surveillance, active monitoring of contacts, infection control measures in hospitals, community education and precaution, the distribution and wearing of masks [3-6]. Among COVID-19 infected individuals, the fatality rate varies across different regions and mainly related to the factors which affect the fatality process.

Epidemiologically, COVID-19 has been mainly described by a reproductive number, disease severity, incubation period and Case Fatality Rate (CFR) or mortality rate. For instance, COVID-19 has been mainly characterized by a low CFR and high transmitted rate (Reproductive number R0) when compared with two predecessors, Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS), which had 10 and 40

CFR for SARS and MERS respectively [7,8]. Many studies confirmed that COVID-19 has a high reproductive number (2-5) [8,9] and more extended incubation periods (1-14 days) [7,10]. Despite the confirming information about COVID-19, there are wide disparities related to the burden of COVID-19 within the countries; therefore, CFR may be related to the health policy measures and population health background of the communities. For example, comorbidity, age and gender distribution are mostly related to hospitalization, number of cases which requires intensive care, and CFR [2,11]. The main comorbidities that associated with COVID-19 were hypertension (53.8%), diabetes (42.3%), and Coronary Heart Disease (CHD) (19.2) [12,13] and older populations such as Italy was also recorded a high CFR, 10.1 [13].

COVID-19 fatality rate is not very high, but this high reproductive number of COVID-19 resulted in more death cases than other coronavirus diseases. Furthermore, a group of Chinese researchers found that the basic reproductive number R (0) of COVID-19 was 2.2 [10,14]. However, the COVID-19 fatality rate was low, but this high reproductive number of COVID-19 resulted in more death cases than SARS, MERS and Ebola [7]. Therefore, specific policies were required to decrease the death consequences [1,13,15,]. COVID-19 is considered of a great importance for the healthcare sectors [16], and the high incidence the rate of COVID-19 overburdens the health system and causes more CFR. CFR is defined as the number of known death cases among the number of confirmed cases [3]. For instance, the observed CFR from Hubei (including Wuhan city) ranged from 3.5% to 12% [16-19], and CFR of COVID-19 in Wuhan city was estimated as the highest, 5.25% [10]. Furthermore, case fatality proportions were 7-fold higher in Hubei in comparison with other regions (2.3) [12,20], and this was mainly related to the high health care system capacity for management of COVID-19 critical cases [21]. For instance, the great demand for medical and intensive cares in Hubei resulted in the high CFR of COVID-19 [3].

In the beginning of the diseases spread in Italy, CFR of COVID-19 was relatively low as in China (2.3%) but after the increase of COVID-19 incidence rate, the CFR rate became much higher [21,22]. Moreover, the health system capacity in Italy was haphazard due to the rapid outbreak, and Intensive Care Unit (ICU) beds were only available to less than 6% of cases [3,23,24]. A similar outcome was also observed in Iran at the start of the outbreak, in which CFR was 2.6; however, some other studies have anticipated that such CFR will be increased with high incidence rate [25]. In this review, fatality rate of COVID-19 in relation to the population health background according to comorbidity, age, gender distribution, and laboratory prognosis for COVID-19 patients. In addition, the assessment of immunological aspects among COVID-19 fatalities for determination of the important indicators that can be used to detect severity cases of the disease.

Methodology

This review aimed to indicate the rate of people who infected with COVID-19 or they are in critical condition as well as the mortality rate and also the factors that are related to morbidity of COVID-19 cases were also analyzed. The method of study is a rapid review study. Convenient data from other studies were retrieved for this review. 487 papers were reviewed in the first screening on PubMed and Web of Science, 60 papers were used in this study. The main keywords have been used to searching papers were COVID 19, CFR, COVID-19 mortalities rate, and epidemiology of COVID-19. This study was aimed to find the epidemiological factors which highly contributed in the morbidity and mortality rates of COVID-19. Fatality rates were assessed by using the epidemiological data and laboratory findings of COVID-19. Data were arranged into two different tables, which describe epidemiological factors and laboratories description that involved in COVID-19 fatalities. The main epidemiological factors which have been recorded for COVID-19 fatalities include gender, age, and comorbidity. The laboratory assessment related to lymphocytes, leukocytes, C-reactive protein (CRP), Erythrocyte Sedimentation Rate (ESR), Lactate Dehydrogenase (LDH) and platelet counts were also analyzed.

Results

Epidemiological Assessment of COVID-19 Fatalities

The collected data on the epidemiological assessment of COVID-19 fatality in (Table 1) illustrated that the fatality rate among infected patients with COVID-19 is associated with comorbidity. For instance, the highest comorbidity prevalence was recorded in the USA and Italy, where was 93.9 and 68%, respectively. Hypertension is considered as the highest comorbidity factor among patients associated with COVID-19 in most of countries and ranged from 11.9% - 67.3%. Furthermore, the comorbidity significantly contributed to the severity and fatality rate of COVID-19 cases. Moreover, COVID-19 severity

rate was slightly higher among cancer patients than diabetic patients; the severity rates were 53% and 45%, respectively. The percentage of patients who requiring ICU varied from 5% to 43.5 %, in which CHD was considered as the most common comorbidity associated factor in ICU. North Korea had a lower CFR, 0.5%. Cardiovascular Disease (CVD) had the highest odds ratio (3.42) from which 49% of the critical cases died. Besides, being male was associated with a high incidence of COVID-19. Most of the studies have revealed that 60% of infected patients were male, while in a study in Italy showed that 82 % of cases were male. The male to female fatality odds ratio was 3.4. Moreover, these findings have revealed that age has an effect on the ICU admission, severity, and fatality rate of COVID-19. The mean age of COVID-19 was 60 years old, and each 5-year increase was associated with a 20% greater risk of death. The fatality rate for the age group of 80-89 years in South Korea, China, and Italy was 8.7%, 14.7%, and 18.8% respectively.

Immunological Assessment of COVID-19 Fatalities

The data on the immunological assessment of COVID-19 fatality in (Table 2) revealed that immunological cells and inflammatory proteins are the leading indicators for the severity of COVID-19. Firstly, lymphocyte count is considered as the main predictor of the prognosis and severity in COVID-19 cases. Furthermore, lymphocytopenia was observed in 91% of COVID-19 death cases, and also lymphocytopenia in 50-82% of COVID-19 infected patients. Moreover, white blood cell (WBC) count was significantly raised in COVID -19 patients, and it was statistically higher among the severe male patients and those who died from COVID-19. For instance, WBC count was 9.8-10.2 $\times 10^9$/L in fatal cases. The increase of WBC and especially neutrophils was associated with heart injury. Also, the high increase of pro-inflammatory indicators was mainly found in COVID-19, and it was significantly higher among the fatal cases. Consequently, the raised pro-inflammatory proteins lead to heart injury and increase the hypersensitive cardiac troponin I level, *p*g/mL (≤ 15.6). CRP had increased by 40- 60% in COVID-19 cases, and it was markedly increased (82%) among COVID-19 cases who suffer from cancer. For platelets count, there was a low significant decrease in infected patients and fatal cases and less than 156 $\times 10^9$/L.

Table 1. Epidemiological assessments of COVID-19 cases and fatality rate in different countries of the world.

References	Place	Study Design	Severe Cases	ICU Cases	CR	CFR	Gender	Age/ CFR
Li H. [31]	Wuhan	Retrospective cohort study *n* = 28 cancer patient	53.6%	35.7%	CVD: 14% DM: 14%	28.6%	M: 60%	65 year
Li LQ [26]	Wuhan	Meta-analysis	------	------	------	7%	M: 60%	> 60 year
Yu L. [27]	Tibetan	Case-Control study *n* = 94 death reported	------	------	HTN: 39:6% DM: 26.2% CHD:14.5%	CHD: 4.2% CNS = 2.9% COPD: 2.6% Renal failure: 2.3% HTN = 1.4% DM: 1.1%	------	> 60 year
Yu L. [28]	Tibetan	Cross sectional study *n* = 94 death reported	------	------	CD: 29.9% HTN:11.9% DM: 5.9% CVD: 4.4%	10%	------	Mean age: 44
Wu C. [29]	China	Retrospective cohort study *n* = 188 patients	------	43.5%	HTN: 20% DM: 10% Smoking: 6.5%	Cardiac issue: 55% CNS = 2.9% COPD: 2.6%	M: 63%	------
Fei Z. [30]	Wuhan	Retro-Cohort study *n* = 191 patients	------	26%	CR: 48% HTN: 31% DM: 19% CVD: 8% COPD: 3%	28.3%	M:62%	------
Li H. [31]	China	Cross sectional study *n* = 5319 patients	------	------	------	1.4%	------	> 40:0.01 > 90: 0.48
Jain V. [32]	Wuhan	Meta-Analysis study *n* =1813 patients	------	------	COPD: 4.5%	6.8%	M rate: 67.2%	Mean age: 62.4
Rubino S. [23]	Italy	Cross sectional study *n* = 94 death reported	------	------	------	6.8%	M: 8.1% F: 5.0%	60-69: 3.2% 70-79: 11.8% 80-89: 18.8% ≥ 90: 21.6%
Jian-Min J. [34]		Case series study *n* = 1056 patients	------	------	HTN: 23% DM: 11.6% CVD: 9%	0.5%	M: 70%	≥ 65 Death: 83.8% Survivor: 13.2%

Table 1 (continued). Epidemiological assessments of COVID-19 cases and fatality rate in different countries of the world.

References	Place	Study Design	Severe Cases	ICU Cases	CR	CFR	Gender	Age/ CFR
Yang J. [35]	Wuhan	Meta-analysis study *n* = 46248 patients	------	------	HTN:17% DM: 8% CVD: 5% RD: 2%	HTN: 2.36% RD: 2.46% CVD: 3.42%	------	> 60 year
Nasiri M. [36]	Tehran	Meta-analysis study	------	------	HTN: 18.5% CVD:14.9% DM: 10.8% Hepatic: 8.1% Smoking: 8%	6.6%	OR:3.4	------
Russell T. [37]	Diamond Princess	Cross sectional study *n* = 619 patients	------	------	------	2.3% CNS = 2.9% COPD: 2.6% Renal failure: 2.3%	------	50-59: 1.3% 60-69: 3.6% 70-79: 8% 80-90: 14.8%
Zhang Y. [38]	Wuhan	Cohort-study *n* = 321 patients	45.0%	21.3%	HTN: 47.3% CVD: 14.9% CNS: 4.4% Renal failure: 3.7%	11%	M: 53.5%	Median age: 64
Guan W. [39]	China	Cross sectional study *n* =1099 patients	15.7%	5%	CR: 23.7% HTN: 15 % DM: 7.4 % CHD: 2.5 %	1.4%	M: 58.1%	Median age: 47
Chen T. [40]	Wuhan	Retrospective case series *n* = 1073 patients	------	------	HTN: 48% DM: 26.2%	------ CNS = 2.9%	M: 73%	Median age: 68
Zhang G. [41]	Wuhan	Retrospective study *n* = 95 patients	------	93%	------	------	M: 26.2% F: 26.2%	< 40: 41.7% 40-60: 27.8% > 60: 41.2%
Wu Z. [42]	China	Retrospective study *n* = 44 672 patients	14%	5%	------	ICU: 49% CVD: 10.5% DM: 7.5% COPD: 6.3% HTN = 6% Cancer: 5.6%	------	70 - 79: 8.0% ≥ 80: 14.8%
KSID [43]	South Korea	Retrospective study *n* = 4,212 patients	------	------	------	0.5%	M: 59.1%	Median age: 63 60-69: 1.1% 70-79: 3.1% 80-90: 8.7%
Grasselli G. [44]	Italy	Retrospective case series *n* = 1591 patients	------	------	HTN: 49% CVD: 21% Lipidemia:18% DM: 17 Cancer: 8%	26%	M: 82%	Median age: 63
Barrasa H. [45]	Spain	Retrospective case series *n* = 45 patients	------	------	HTN = 44% COPD: 38% DM: 19% Cardiac: 10%	13%	M: 56%	Mean age: 67
Richardson S. [46]	USA	Case series study *n* = 5700 patients	------	6.5 %	CR: 93.9% HTN: 56.6% CVD: 18% DM: 33.8% Obesity:19% Cancer: 6%	9%	M: 60.3%	Mean age: 63
McMichael T. [47]	USA	Retrospective case series *n* = 167 patients	39.5%	------	HTN = 67.3% CVD: 60.4% Renal failure: 40 DM: 31.8% RD: 31.7% Obesity :30 % Cancer: 14 %	33.7%	M: 33%	Mean age: 72

CFR: case fatality rate; HR: hazard ratio; OD: odd ration; M: male; F: female; comorbidity rate: CR; chronic disease: CD; HTN: hypertension; DM: Diabetic mellitus; CVD: cardiovascular diseases; COPD: Chronic obstructive pulmonary disease; respiratory disease: RD; CNS: central nervous system; ICU: intensive care unit.

Table 2. Immunological assessments of COVID-19 cases and fatality rate in different countries of the world.

References	Place	Study Design	Lymphocyte count	WBC and ESR	CRP	Platelets count	Fatality Rate
Zhang L. [25]	Wuhan	Retrospective cohort study *n*= 28 patients	Lymphopenia: 82%	↑ ESR (57%)	↑ CPT:82% ↑ LDH: 50% ↑ D-Dimer: 39.3%	------	28.6%
Li LQ [32]	Wuhan	Meta-analysis	Lymphocytopenia: 64 Leukocytopenia: 29.4%	------	↑ CRP: 44.3% ↑ LDH 28.3%	------	7%
Yu L. [28]	Tibetan	Cross sectional study *n*= 67 patients	Symptomatic: $1.6\pm0.5\times10^9$/L Asymptomatic: $1.3\pm0.6\times10^9$/L	Normal WBC Symptomatic: 5.5±1.4 Asymptomatic: 6.3±2	Pre-albumin level Symptomatic: 1.6±0.5 Asymptomatic:1.3±0.6	Symptomatic:149.3 Asymptomatic:153.5	28.6%
Wu C. [29]	China	Retrospective cohort study	↓ lymphocytes and monocytes	↑ WBC and neutrophil	↑ IL-6 and CRP	------	55%
Fei Z. [30]	Wuhan	Retro-Cohort study	Non-survivor: 0.6×10^9/L Survivor: 1.1×10^9/L	WBC ($\times10^9$/L) ↑ WBC	↑ LDH ↑ D-dimer ↑ IL-6	Non-survivor: 165·5 Survivor: 220·0	28.6%
Jian-Min J. [34]	------	Case series study *n*:43 patients	$1.0\pm0.4\times10^9$/L Leukocytopenia: 29.4%	WBC: 6.8±2.2 M: 7.7±2.3	LDH: 369.4±132.7 ↑ LDH 28.3%	225.2	0.5%
Nasiri M. [36]	Tehran	Meta-analysis *n* = 94 death reported	Lymphopenia: 50% Leukocytopenia: 29.4%	↑ ESR: 79% ------	↑ CRP: 72% ↑ LDH: 41%	11.1%	6.6%
Zhang Y. [38]	Wuhan	Cohort-study	Lymphocytes: 1.01×10^9/L Neutrophil: 3.92×10^9/L	WBC: 5.64×10^9/L	CRP: 30.75 LDH: 268.5 D-Dimer : 0.56	36.75	11%
Guan WJ [39]	China	Cross sectional study	Lymphocytopenia: 83.2% Neutrophil: 3.92×10^9/L	WBC Per/mm^3: 4700 Leukopenia: 33.7%	↑ CRP: 60% ↑ LDH: 41% D-dimer: 46.4%	Per/mm^3: 168000 thrombocytopenia	1.4%
Chen T. [40]	Wuhan	Retrospective case series *n*: 1073 patients	In death: 91% In recovery: 47%	Death: 10.2×10^9/L Recovery: 5.0×10^9/L	Death case: 564.5 LDH Recovery case: 268	Death: 156×10^9/L Recovery:198×10^9/L	------
Zhang G. [41]	Wuhan	Retrospective study *n*: 95 patients	<0.4* 10^9/L Neutrophil: 3.92×10^9/L	WBC: ≤ 10 * 10^9/L Neutrophil: ≤7 * 10^9/L	CRP level: <10 mg/L LDH <245 U/L D-dimer level: 33.6%	11.6%	------
Tan L. [48]	China	Retrospective case series *n*: 92 patients	Severe cases: < 20% Moderate case: > 20%	Death: 10.2×10^9/L Recovery: 5.0×10^9/L	Death case: 564.5 LDH Recovery case: 268	Death: 156×10^9/L Recovery:198×10^9/L	
Richardson S. [46]	USA	Case series study *n*: 5700 patients	0.88 $\times10^9$/L Neutrophil: 3.92×10^9/L	WBC: 7.0×10^9/L Neutrophil: 5.3×10^9/L	CRP: 13.0 LDH: 404.0 D-dimer: 438	------	9%

WBC: white blood cell; LDH: Lactate dehydrogenase; CRP: C-reaction protein; ↓: decease and ↑: increase.

Discussion

Epidemiological Analysis of COVID-19 Fatality Rate

The present review was based on data from the copious studies that had homogeneity to the review's objectives. It included the newest studies from December 2019 to April 2020. In this review, epidemiological factors were analyzed for high morbidity and mortality rates among COVID-19 patients. Furthermore, the fatality rate of COVID-19 and its relation to the confounding effects of age, gender, other comorbidities, and immunological conditions of COVID-19 patients were analyzed. The mortality rate of COVID-19 is more related to chronic conditions among COVID-19 patients such as hypertension, diabetes and long-term therapy of cancer patients. The death rate is high among patients who are treated with high blood pressure medication. This may due to using the receptor, angiotensin-converting enzyme 2 (ACE2) by the virus and it is also a target for the hypertension medication. The death rate among cancer patients may also be related to using immunosuppressant medicines that lead to immune deficiency.

In Germany, the cases of COVID-19 have more comorbidities in comparison with China, and the proportions were (70% - 77%) and (20% - 51%), respectively [15]. Furthermore, another study in China has illustrated that 14% of COVID-19 cases were severe and caused pneumonia, from which about 5% of patients had the acute disease in the ICU [7,20]. Regarding the disease severity, another study in China illustrates that about 80% of COVID-19 cases had a mild to moderate stage of the disease with symptoms of fever and dry cough, 13.8% of them had severe symptoms, and 6.1% had life-threatening episodes of respiratory failure, septic shock, or organ failure. Moreover, an investigation has shown that 50 - 70% of COVID-19 cases were asymptomatic at the time of diagnosis [9]. A review has elucidated that about 20.3% of hospitalized patients who requires ICU, 13.9% of them were fatal cases, 32.8% had Acute Respiratory Distress Syndrome (ARDS), 6.2% with shock [50]. Low severity of cases have been observed in Italy; for instance, almost (9 -11%) of COVID-19 cases were admitted into the ICU [51]. It can be summarized that the death is obvious in those patients who are infected severely by COVID-19 and more common among those people who suffer from chronic disease conditions. Moreover, the result of the death is more related to the respiratory failure, septic shock, and/or other organ failures.

It is observed that the CFR of COVID-19 is high and may be more related to the prospective comorbidities among the infected patients [21,52]. The current review has found that the mortality of COVID-19 is almost associated with comorbidity among the patients who infected with COVID-19. The highest rate of comorbidity was observed in developed countries, such as USA and Italy, and was 93.9 and 68%, respectively. Chronic infections can be counted as an enhancing factor for comorbidity, in which hypertension recorded the most dominant reason than other comorbidities. In addition, comorbidity had an impact on both severity and fatality rate and particularly in the USA and Italy. Moreover, most of the COVID-19 severe cases were observed among cancer and diabetic patients, with 53% and 45%, respectively. In addition, the ICU requirement rate was ranged from 5% to 43.5 %, in which most of the cases were related to CVD comorbidity, and CVD odd ratio for CFR was highest 3.42 among other comorbidities. However, a low CFR (0.5%) of COVID-19 cases was observed in the Republic of South Korea and the correlation between comorbidities and COVID-19 CFR has been measured in the study using the Odds Ratio (OR), and it showed that there is a positive association between the presence of comorbidities and COVID-19 CFR (OR = 1.709) [53].

The age factor is also vital in the detection of fatalities among COVID-19 cases and it varies between the countries. For instance, Italy is one of the countries with a large number of older people; 23.3% of its population is more than 65 years old, but in China, this age group is around 12% [21,34]. Furthermore, the CFR of COVID-19 cases was significantly high in the age of 80 years (21.9%) [50]. However, the CFR of COVID-19 cases among Chinese population with age group less than 30 years and more than 59 years was 0.6 and 5.1, respectively [51]. For determining the correlation of age with CFR of COVID-19, a multivariate regression analysis has been measured which indicated that age factor with (OR = 1.038) was considered as the risk factor of the severity of COVID-19 death [52]. In South Korea and Australia, the most affected patients were aged in the 20s and 50s year [27], and CFR is significantly increased with older age group. For example, CFR was 1.2 and 0.2 young age group (< 50 years) and old age group (≥ 50 years) respectively [53].

Moreover, almost all patients aged more than 65 years usually require ICU admission [54]. The current review has illustrated that age factor is significantly contributed to ICU admission, severity and fatality rate; and among the older age group; for each 5-year-

increase, there was a positive association with 20% risk of fatality. While, there was a slight variation in CFR for the age group of 80-89 years in Korea, China and Italy, which were, 8.7%, 14.7% and 18.8%, respectively.

The fatality rate of COVID-19 was higher among males rather than females, and the reason behind this difference is still unknown [55] but smoking and severity of comorbidities are higher among the males than females [37]. Moreover, the presence of X chromosome and sex hormones on the innate and adaptive immunities may have more protection role to females against viral infection [27,56,58]. Furthermore, due to the high level of circulating ACE2 levels in males; therefore, they are more at risk for COVID-19 because of SARS-CoV-2 attacks the respiratory cells through ACE2 receptors. These reasons may have an effect on male to have the higher mortality rate among patients with COVID-19 [35]. The current review revealed that the male patients are almost associated with the high incidence of COVID-19, from which 60% of COVID-19 infected patients were male, and in Italy, the male rate was even higher (82 %), and the male to female fatality odd ratio was 3.4.

Immunological Description of COVID-19 Fatalities

In the current review, it has been shown that there is a relation between immunological cells and pro-inflammatory proteins and COVID-19 severity rate. For instance, lymphocyte count has indicated the severity and prognosis of COVID-19. Lymphocytopenia has also been observed in 91% of COVID-19 death cases, and 50-82 % of COVID-19 patients. Furthermore, WBC count was significantly higher in COVID -19 patients, and particularly in severe patients who were mostly male, and in fatal cases. WBC count was 9.8-10.2 $\times 10^9$/L in dead patients, and the increased number of WBC and especially neutrophils may induce heart injury and pro-inflammatory proteins and lead to heart injury and increase the hypersensitive cardiac troponin I level. Moreover, CRP had increased in 40-60% of COVID-19 patients, and particularly among those who have cancer, 82%. The low platelet counts (less than 156 $\times 10^9$/L) contributed to increase the fatality rate of COVID-19. A low ability of the immune system is observed among COVID-19 patients, and this may be due to that the numbers of WBC, lymphocytes, and platelets in COVID-19 are lower than the standard ranges [43,57]. Also, the inflammatory process is also initiated by the increased CRP and D-dimer level, and this aggravation process continues by the release of the cytokine storm including interleukins (IL1B, IL1RA, IL7, IL8) [55-58]. The increased pro-inflammatory cytokines rate may cause a tissue injury in the heart, liver and kidney, and consequently results in fatal outcome among server and critical cases of COVID-19 [30].

The immune system is considered as the most intrinsic body responses to infectious diseases, but it is highly variable among individuals and communities. In this review, the analysis and determination of these immuno-response variability and their relationship to the fatality process in different communities and region have been reviewed. Until now, there is not enough investigation into the immunological process of COVID 19 in European countries. Therefore, this review has a limitation related to the analysis of the immunological causes of COVID 19 fatalities among different countries.

Conclusions

COVID-19-is a new respiratory disease that has spread throughout the world. The disease can cause death in some patients who infected severely with COVID-19. Fatality of COVID-19 is more common among the older age patients and who suffer from chronic diseases. In general, many factors may contribute to the severity and fatality rates of COVID-19 such as comorbidity, age, and gender. The highest rate of comorbidity prevalence was observed in developed countries such as the USA and Italy. The mean age of the most COVID-19 fatalities was more than 60 years old. Gender may has a role in comorbidity and mortality and it is more observed among male patients. In the USA, comorbidity is the most counted cause of death among COVID-19 cases. In respect to immunological aspects, lymphocytopenia was observed in most of the death cases; therefore, it is counted as one of the factors that increase the mortality rate among COVID-19 cases. This review recommends to follow the preventive measures for overcoming the challenges that faced during this emerging pandemic disease.

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