



Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.



Co-morbidity and blood group type risk in coronavirus disease 2019 patients: A case–control study

Mohammed Badedi^{a,*}, Ali Makrami^b, Awaji Alnami^b

^a Administration of Research & Studies, Jazan Health, Saudi Arabia

^b Jazan Health Affairs, Saudi Arabia

ARTICLE INFO

Article history:

Received 10 November 2020

Received in revised form

23 December 2020

Accepted 29 December 2020

Keywords:

Comorbidity

Blood type

ABO blood groups

SARS-CoV-2

COVID-19

ABSTRACT

Objective: The objective of the study was to assess mortality risk associated with co-morbidities and blood group type in coronavirus disease 2019 (COVID-19) patients in Jazan, Saudi Arabia.

Methods: This case–control study enrolled 323 Saudi adults with COVID-19, confirmed by real-time reverse transcription–polymerase chain reaction. The participants were selected randomly between August 31, 2020, and July 1, 2020, from the Health Electronic Surveillance Network system, which contains the primary data on COVID-19 infections in Jazan, Saudi Arabia. The sample included 108 patients who died due to COVID-19 disease and 215 controls who recovered from it (1:2 ratio). The chi-square test, independent samples t-test, and logistic regression were used to perform the statistical analysis.

Results: Mortality was higher in older age patients with COVID-19 (mean = 65.4 years, standard deviation [SD] = 15.6) compared to recovered patients (mean = 39.5 years, SD = 14.8) ($p < 0.001$) with a moderate effect size (eta squared = 0.06). Diabetes mellitus (odds ratio [OR] = 9.4), hypertension (OR = 8.6), cardiovascular disease (OR = 7.4), chronic kidney disease (OR = 3.3), and obesity (OR = 2.0) were significantly associated with death due to COVID-19. Using logistic regression analysis, older age and diabetes mellitus were the primary independent predictors of COVID-19 mortality. However, there was no significant association between a specific ABO blood group and mortality risk ($P = 0.07$).

Conclusion: Older age and the presence of co-morbidities, especially diabetes mellitus, increased the risk of death in patients with COVID-19. Establishing the causality of death in patients with COVID-19 should be a key aim of future studies.

© 2021 The Author(s). Published by Elsevier Ltd on behalf of King Saud Bin Abdulaziz University for Health Sciences. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Introduction

The novel coronavirus disease 2019 (COVID-19), a pandemic infectious disease, is caused by severe acute respiratory syndrome coronavirus-2 [1]. It has spread rapidly across the globe, infecting over 30 million people, and, by September 25, 2020, had caused over one million deaths [1]. On this date, the Saudi Ministry of Health reported over 11,000 confirmed cases of COVID-19 infection in the Jazan region, south west of Saudi Arabia [2]. The risk

factors associated with mortality due to COVID-19 have not been adequately assessed. Some studies have indicated that the elderly and those with co-morbidities, such as diabetes, hypertension, and heart disease, are at considerable risk of death due to COVID-19 [3–6]. Furthermore, few studies in descriptive design tried to explore the association between ABO blood groups and death due to COVID-19 [7–9]. Some studies have identified an association between blood group type A and disease mortality in COVID-19 patients [7,8]. However, others have not found any association between blood group and mortality risk in patients with COVID-19 [9].

Further studies in analytical design, are required to assess the risk of co-morbidities and other factors on the prognosis of COVID-19 patients owing to genetic and ethnic differences among populations and the paucity of data in this regard. In addition, to the best of our knowledge, no study has yet been carried out to evaluate this association in Jazan, Saudi Arabia. Therefore, the current study's objective was to evaluate the association between co-morbidities

Abbreviations: ACE2, Angiotensin-converting enzyme 2; BMI, Body mass index; COVID-19, Coronavirus disease 2019; CVD, Cardiovascular disease; CKD, Chronic kidney disease; HESN, Health Electronic Surveillance Network; OR, Odds ratio; PCR, Real-time reverse transcription–polymerase chain reaction; SD, Standard deviation; T2DM, Type 2 diabetes mellitus.

* Corresponding author.

E-mail addresses: dr.badedi@gmail.com (M. Badedi), dr.ali.omfs.e@gmail.com (A. Makrami), aal-naami@moh.gov.sa (A. Alnami).

<https://doi.org/10.1016/j.jiph.2020.12.035>

1876-0341/© 2021 The Author(s). Published by Elsevier Ltd on behalf of King Saud Bin Abdulaziz University for Health Sciences. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

and blood type and increased risk of death in Saudi patients with COVID-19 in Jazan, Saudi Arabia.

Method

Study design and population

This case–control study was conducted on Saudi patients with COVID-19 in Jazan Region, located in southwestern Saudi Arabia and characterized by a relatively homogenous population with similar ethnic and socioeconomic characteristics [10–14].

Sampling technique

The study sample comprised patients diagnosed with COVID-19 between August 31, 2020, and July 1, 2020, identified through the Health Electronic Surveillance Network (HESN) system, the country's official central epidemiological surveillance program and the main source of data for patients infected with COVID-19 in Jazan. Patients who died ($n = 159$) and those who recovered from COVID-19 ($n = 11,227$) were included in two sampling frames as the case and control groups, respectively. Participants were selected randomly from the sampling frames using simple random technique (Fig. 1).

Sample size

The sample size was estimated using Epi Info™ [15] and the following parameters: 95% confidence interval (CI), power of 80%, and a case–control ratio of 1:2. A hypothetical assumption of risk (40%) was applied to the control group, and an odds ratio (OR) of 2.0 was used in the calculation. The procedure yielded a total sample size of 323; there were 108 patient deaths (cases) and 215 patient recoveries (controls).

Definitions

The study participants were patients in whom a diagnosis of COVID-19 infection was confirmed following the identification of viral RNA in a nasopharyngeal swab sample using real-time reverse transcription–polymerase chain reaction (PCR) (LightCycler® 480 Instrument II, Roche) [16]. The criteria for recovery were based on the guidelines of the Ministry of Health, Saudi Arabia; recovery was considered to have occurred when at least three days had passed after the resolution of fever and respiratory symptoms and after obtaining two negative PCR samples results taken ≥ 24 h apart; alternatively, at least 10 days had to have passed since symptom onset [17].

Data collection

The data were collected retrospectively from the patients' health records and included their demographic characteristics, anthropometric and laboratory measurements, age, sex, smoking history, COVID-19 clinical symptoms and outcomes, co-morbidities, body mass index (BMI), and blood type (ABO blood group system). Co-morbidities included cardiovascular disease (CVD), chronic kidney disease (CKD), diabetes mellitus (DM), hypertension, and obesity. The clinical symptoms of COVID-19 included fever, cough, shortness of breathing (dyspnea), loss of taste and smell (anosmia), chest pain, sore throat, congestion, a runny nose, fatigue, headache, diarrhea, and vomiting. ABO blood type identification was determined using ID-Centrifuge® 12 S II (Bio-Rad) [18]. In keeping with the Worldwide Health Organization guidelines [19], BMI was calculated as weight in kilograms divided by the square of the person's height in meters. A BMI score of ≥ 30 was categorized as obese.

Statistical analysis

Data entry and analysis were performed using Statistical Package for the Social Sciences® software [20]. The data were coded with anonymous identification numbers to ensure the privacy of the participants. The continuous variables were described as means

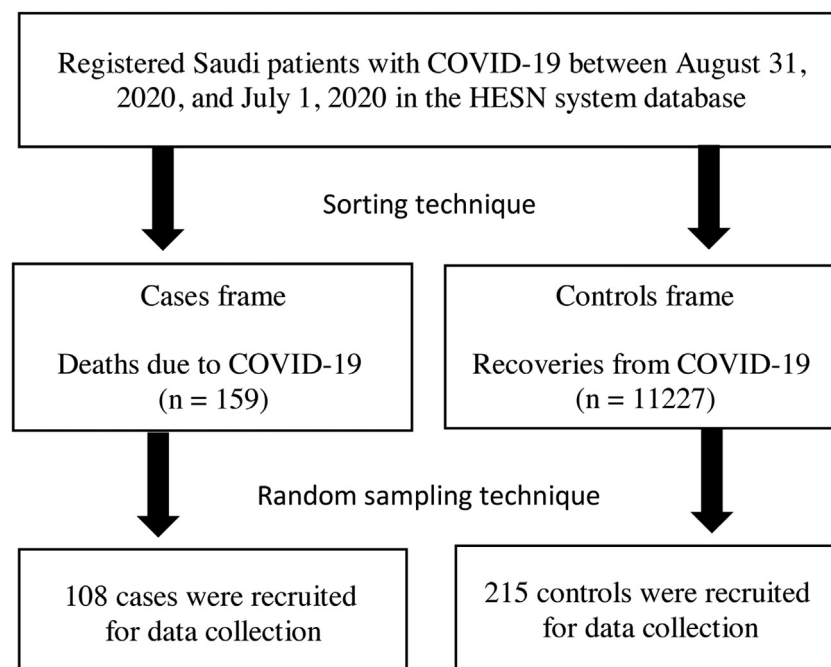


Fig. 1. Patient enrolment and the sampling technique in the current study.

Table 1
Demographics and clinical characteristics of the study population.

Factor	Overall (n = 323)	Recovered (n = 215)	Deaths (n = 108)	P
Age				
Mean ± SD	49.0 ± 19.6	39.5 ± 14.8	65.4 ± 15.6	<0.001*
Sex				
Male	195 (60.4%)	134 (62.3%)	62 (57.4%)	0.28
Female	128 (39.6%)	81 (37.7%)	46 (42.6%)	
Smoking				
No	287 (88.9%)	183 (85.1%)	103 (95.4%)	0.001*
Yes	36 (11.1%)	32 (14.9%)	5 (4.6%)	
Clinical symptoms				
No	24 (7.4%)	25 (11.6%)	0	<0.001*
Yes	299 (92.6%)	190 (88.4%)	108 (100%)	
Cardiovascular diseases				
No	276 (85.4%)	203 (94.4%)	75 (69.4%)	<0.001*
Yes	47 (14.6%)	12 (5.6%)	33 (30.6%)	
Hypertension				
No	203 (62.8%)	170 (79.1%)	33 (30.6%)	<0.001*
Yes	120 (37.2%)	45 (20.9%)	75 (69.4%)	
Diabetes mellitus				
No	201 (62.2%)	173 (80.5%)	33 (30.6%)	<0.001*
Yes	122 (37.8%)	42 (19.5%)	75 (69.4%)	
Chronic kidney disease				
No	305 (94.4%)	208 (96.8%)	97 (89.8%)	<0.002*
Yes	18 (5.6%)	7 (3.2%)	11 (10.2%)	
BMI				
Not obese	231 (71.5%)	166 (77.2%)	68 (63.0%)	0.002*
Obese	92 (28.5%)	49 (22.8%)	40 (37.0%)	
Blood type O	212 (65.6%)	134 (62.3%)	77 (71.3%)	0.07
Blood type A	78 (24.1%)	55 (25.6%)	23 (21.3%)	
Blood type B	29 (9.1%)	22 (10.2%)	8 (7.4%)	
Blood type AB	4 (1.2%)	4 (1.9%)	0	

* Significant results (P value <0.05).

± standard deviation (SD), and the categorical variables were presented as percentages and frequencies. The chi-square test and fisher's exact test were used to assess any significant associations between the categorical variables. Independent-samples t-test was performed to determine mean differences between the groups. Logistic regression analysis was employed to identify predictors of COVID-19 mortality. A P-value of <0.050 was considered to be statistically significant.

Results

Three hundred and twenty-three individuals with COVID-19 were recruited in the current study. One hundred and eight patients demised due to COVID-19, and 215 recovered from the disease. The participants' sociodemographic characteristics and clinical comorbidities are depicted in [Table 1](#). The mean age of those who died and those who recovered was 65.4 years (SD = 15.6) and 39.5 years (SD = 14.8), respectively (a respective age range of 25–101 and 13–81 years) ([Table 1](#)). An independent samples t-test was used to identify the mean differences in age between the two groups of participants with COVID-19 (Group 1, the patients who died and Group 2, the patients who recovered). A statistically significant difference in mean age was found between the Group 1 and 2 patients ($p \leq 0.001$); older age was significantly associated with mortality, with a moderate effect size (eta squared = 0.06, 95% confidence interval [CI]: –28.69 to –23.18).

Men were more likely than women to be infected with COVID-19 and represented the highest percentage of deaths and recoveries; however, a significant association was not found between sex and death due to COVID-19 ([Table 1](#)). The highest percentage of those who recovered smoked, comparative to those who died (i.e., primarily the elderly) who did not smoke frequently. All the patients who died (100%) experienced severe COVID-19 clinical symptoms. The majority of those who recovered (88.5%)

Table 2
Predictors of death related to COVID-19 using logistic regression analysis.

Predictor	P-value	OR	(CI 95%)
Age	<0.001*	1.1	(1.07–1.11)
Obesity	0.07	1.6	(0.59–2.25)
CVD	0.16	1.7	(0.95–3.01)
Diabetes mellitus	0.01*	2.4	(1.21–4.60)
Hypertension	0.12	1.7	(0.86–3.73)
Kidney disease	0.46	1.4	(0.55–3.81)

* Significant results (P value <0.05).

had clinical COVID-19 symptoms, and the remainder (11.5%) were asymptomatic ([Table 1](#)).

COVID-19 patients with co-morbidities were demonstrated to be at greater risk of mortality than others ([Table 1](#)). Patients with diabetes mellitus and hypertension were more than nine times at greater risk of dying than others (OR = 9.4 and 8.6, respectively, both with a large effect size: phi = 0.5). Compared to others, the risk of dying was seven times higher (OR = 7.4, medium effect size phi = 0.5) for COVID-19 patients with cardiovascular disease (CVD) and three times higher (OR = 3.3, small effect size: phi = 0.1) for such patients with chronic kidney disease (CKD). The BMI values (mean ± SD) for demised patients and those who recovered were 27.8 ± 6.1 and 26.8 ± 5.9, respectively (a respective range of 14–48 and 13–46). Obese patients with COVID-19 were at twice as likely to die than patients who were not obese (OR = 2.0, small effect size: phi = 0.1).

A statistically significant association between blood group and the COVID-19 patients who died and those who recovered was not determined using the chi-square test ([Table 1](#)) and Yates's correction for continuity. There was no significant association between a specific ABO blood group and mortality risk (P = 0.07).

Logistic regression was performed to assess predictors of mortality among COVID-19 patients. The significant risk factors were then evaluated using the chi-square test ([Table 2](#)). Old age and

diabetes mellitus were established to be the most prominent predictors of death due to COVID-19.

Discussion

COVID-19 is a novel disease, to the best of our knowledge, the current study is the first study to assess the risk of co-morbidities in patients with COVID-19 in Jazan Region, Saudi Arabia. In the current study, older age was found to be an independent predictor of mortality in patients with COVID-19, which is consistent with the results of other studies [5,21,22]. This finding could be explained by the fact that the elderly has a less robust immune response, which places them at severe risk of death due to COVID-19 infection [23,24]. There was no significant association between COVID-19 mortality and sex in the current study. The highest proportion of patients who recovered were smokers; a possible explanation for this is that deaths due to COVID-19 were highest in elderly people who did not smoke frequently in keeping with Saudi Arabian culture. Although the majority of recovered patients with COVID-19 had symptoms that included fever, cough, and dyspnea, 11.5% of them were asymptomatic. However, 100% of the mortalities were symptomatic.

Co-morbidities were also significantly associated with COVID-19 mortality in the present study. The focus was on co-morbidities that included diabetes, hypertension, CVD, CKD, and obesity as they were the most prevalent in COVID-19 patients with disease severity (i.e., exacerbated lung injury and death) [4,25]. Certain co-morbidities were associated with strong angiotensin-converting enzyme 2 (ACE2) receptor expression. ACE2, a cleavable, extracellular enzyme located on the cell surface membrane, mediates entry by SARS-CoV-2 into human cells, leading to significant morbidity and mortality [26].

In the current study, diabetes mellitus was identified as the most significant co-morbidity (with a high OR = 9.4) associated with COVID-19 mortality. People with diabetes are susceptible to SARS-CoV-2 infection due to impaired phagocytic cell capabilities, in addition to several risk factors, including elevated ACE2 receptors levels, impaired T-cell function, and increased interleukin-6 concentration, which enhances viral entry into the cells, resulting in an escalation in lung inflammation and poor outcomes [26]. Although diabetes was independently associated with COVID-19 mortality in the current study, other co-morbidities, including hypertension, CVD, CKD, and obesity, were also linked to COVID-19 deaths, and the synergistic effect of these factors may have contributed to promoting COVID-19 mortality. Similar results were observed in other studies [22]. Our findings are supported by evidence that persistent hypertension is associated with diabetes; in combination, along with metabolic changes, they cause microvascular and macrovascular complications, ultimately leading to CVD, all of which increases the risk of death in patients with COVID-19 [27]. Similar findings were reported by Ma et al. [28]. Patients with hypertension using ACE2 inhibitor medication may be at increased risk of SARS-CoV-2 infection, severe lung injury, and respiratory failure [29].

The findings of the current study also indicated that obesity contributed to COVID-19 patient mortality. A study by Richardson et al. showed that 41.7% of obese patients had severe COVID-19 symptoms and poor outcomes [30] because obesity is associated with reduced oxygen saturation in the blood as a consequence of compromised ventilation at the base of the lungs, low-grade inflammation (i.e., the abnormal secretion of cytokines and adipokines), and interferon consequences in compromised immune response [26].

Blood groups were not associated with COVID-19 patient mortality in the current study, these results are consistent with the

findings of a USA study that reported that no association was found between blood group and risk of death in COVID-19 patients [9]. In Turkey, the highest prevalence of COVID-19 was identified in patients with type A blood (57%), and these patients were considered to be more likely to be infected with severe COVID-19 [7]. Similarly, in Wuhan, China, type A blood was observed to correlate with the highest prevalence of COVID-19 infection (42.8%), and an association was seen between type A blood and severity of COVID-19 [8]. However, this difference might have been owing to the frequency and prevalence of blood groups other than increased risk of COVID-19 deaths.

Conclusion

Older age and the presence of co-morbidities, especially diabetes mellitus, increased the risk of death in patients with COVID-19. However, blood groups were not associated with COVID-19 patient mortality. Establishing the causality of death in patients with COVID-19 should be a key aim of future studies.

Availability of data

The data that support the findings of this study are available on request from the corresponding author, [Mohammed Badedi].

Funding

No funding sources.

Competing interests

None declared.

Ethics approval and consent to participate

The Jazan Health Institutional Review Board (Reference number: H-10-Z-073) granted ethical approval (No. 2030) for the study to be conducted, and the research complied with the Declaration of Helenski. Consent was obtained from all the participants before enrolment.

Authors' contributions

All authors contributed equally in the research steps: study design, data collection, statistical analysis, and writing the manuscript.

Acknowledgments

We would like to express our gratitude to the team who helped us in completing this research. We would like also to thank all participants for their response and cooperation.

References

- [1] World Health Organization (WHO). Coronavirus disease (COVID-19): weekly epidemiological update. Geneva: WHO; 2020.
- [2] Ministry of Health (MOH). Coronavirus disease (COVID-19): daily report update. Riyadh: MOH; 2020.
- [3] Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *JAMA* 2020;323:1061–9.
- [4] Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* 2020;395:1054–62.
- [5] Zhang Y, Cui Y, Shen M, Zhang J, Liu B, Dai M, et al. Association of diabetes mellitus with disease severity and prognosis in COVID-19: a retrospective cohort study. *Diabetes Res Clin Pract* 2020;165:108227.

- [6] Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir Med* 2020;8:475–81.
- [7] Göker H, Aladağ Karakulak E, Demiroğlu H, Ayaz C, Büyükaşık Y, İnkaya A, et al. The effects of blood group types on the risk of COVID-19 infection and its clinical outcome. *Turk J Med Sci* 2020;50(4):679–83.
- [8] Fan Q, Zhang W, Li B, Li D, Zhang J, Zhao F. Association between ABO blood group system and COVID-19 susceptibility in Wuhan. *Front Cell Infect Microbiol* 2020;10:404.
- [9] Latz C, DeCarlo C, Boitano L, Png C, Patell R, Conrad M, et al. Blood type and outcomes in patients with COVID-19. *Ann Hematol* 2020;99(9):2113–8.
- [10] Badedi M, Darraj H, Hummadi A, Najmi A, Solan Y, Zakry I, et al. Khat Chewing and Type 2 Diabetes Mellitus. *Diabetes Metab Syndr Obes* 2020;13:307–12.
- [11] Darraj H, Badedi M, Poore K, Hummadi A, Khawaji A, Solan Y, et al. Vitamin D deficiency and glycemic control among patients with type 2 diabetes mellitus in Jazan City, Saudi Arabia. *Diabetes Metab Syndr Obes* 2019;12:853–62.
- [12] Alzughbi T, Badedi M, Darraj H, Hummadi A, Jaddoh S, Solan Y, et al. Diabetes-related distress and depression in Saudis with type 2 diabetes. *Psychol Res Behav Manag* 2020;13:453–8.
- [13] Badedi M, Darraj H, Hummadi A, Solan Y, Zakri I, Khawaji A, et al. Vitamin B12 deficiency and foot ulcers in type 2 diabetes mellitus: a case-control study. *Diabetes Metab Syndr Obes* 2019;12:2589–96.
- [14] Badedi M, Solan Y, Darraj H, Sabai A, Mahfouz M, Alamodi S, et al. Factors associated with long-term control of type 2 diabetes mellitus. *J Diabetes Res* 2016;8. Article ID 2109542.
- [15] Dean A, Arner T, Sunki G, Friedman R, Lantinga M, Sangam S, et al. Epi Info program for public health professionals. Atlanta: CDC; 2011.
- [16] LightCycler® 480 Instrument II. (n.d.). Retrieved January 14, 2021, from <https://lifescience.roche.com/products/lightcycler-480-instrument-ii>.
- [17] Saudi Center for Disease Prevention and Control, Riyadh COVID-19 guidelines; 2020.
- [18] Bio-Rad©, Cressier Switzerland.
- [19] World Health Organization (WHO). Physical status: the use and interpretation of anthropometry: report of a WHO Expert committee. Technical report series 854. Geneva: WHO; 1995.
- [20] BM Corp. IBM SPSS statistics for windows. NY: IBM Corp; 2012.
- [21] Wu C, Chen X, Cai Y, Zhou X, Xu S, Huang H, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. *JAMA Intern Med* 2020;180(7):934–43.
- [22] Shil Q, Zhang X, Jiang F, Zhang X, Hu N, Bimu C, et al. Clinical characteristics and risk factors for mortality of COVID-19 patients with diabetes in Wuhan, China: a two-center, retrospective study. *Diabetes Care* 2020;43(7):1382–91.
- [23] Goronzy J, Fang F, Cavanagh M, Qi Q, Weyand C. Naive T cell maintenance and function in human aging. *J Immunol* 2015;194(9):4073–80.
- [24] Opal S, Girard T, Ely E. The immunopathogenesis of sepsis in elderly patients. *Clin Infect Dis* 2005;41(7):504–12.
- [25] Guan W, Liang W, Zhao Y, Liang H, Chen Z, Li Y, et al. Comorbidity and its impact on 1590 patients with Covid-19 in China: a nationwide analysis. *Eur Respir J* 2020;55(5):2000547.
- [26] Ejaz H, Alsrhani A, Zafar A, Javed H, Junaid K, Abdalla A, et al. COVID-19 and comorbidities: deleterious impact on infected patients. *J Infect Public Health* 2020;1876-0341(20), 30594-3.
- [27] Lippi G, Wong J, Henry B. Hypertension and its severity or mortality in Coronavirus Disease 2019 (COVID-19): a pooled analysis. *Pol Arch Intern Med* 2020;130:304–9.
- [28] Ma L, Chen W, Gao R, Liu L, Zhu M, Wang Y, et al. China cardiovascular diseases report 2018: an updated summary. *J Geriatr Cardiol* 2020;17(1):1–8.
- [29] Fang L, Karakiulakis G, Roth M. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? *Lancet Respir Med* 2020;8(4):e21.
- [30] Richardson S, Hirsch J, Narasimhan M, Crawford J, McGinn T, Davidson K, et al. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York city area. *JAMA* 2020;22(April).