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ORIGINAL ARTICLE

An investigation of risk factors of in-hospital death due to COVID-19: a case-control study in Rasht, Iran

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Abstract

Background Identifying the non-survived patients' characteristics compared to survived subjects and introducing the critical risk factors of COVID-19 mortality would help enhance patients' prognosis and treatment.

Methods In the current case-control study, medical records of 103 non-survived COVID-19 patients (cases) and 147 sex-matched survivors (controls) who admitted to Razi University Hospital in Rasht, Guilan, Northern Iran from April 21 to August 21, 2020, were explored. Data on demographic, anthropometric, clinical, and laboratory assessment was extracted from the electronic medical records. To estimate the association between variables of interest and mortality odds due to COVID-19 logistic regression was carried out.

Results The patients who died (mean age = 62.87 years) were older than the discharged patients (57.33 years; *P* value = 0.009). According to the results of multivariable regression adjusted for potential confounders, elevated BMI (OR = 2.49; 95% CI = 1.15–5.41), higher CRP levels (OR = 2.28; 95% CI = 1.08–4.78), increased FBS levels (OR = 2.88; 95% CI = 1.35–6.17), higher levels of total cholestrol (OR = 2.55; 95% CI = 1.19–5.45) and LDL (OR = 2.27; 95% CI = 1.07–4.79), elevated triglyceride (OR = 5.14; 95% CI = 2.28–11.56), and raised levels of D-dimer (OR = 5.68; 95% CI = 2.22–14.49) were identified as independent risk factors of COVID-19 mortality. No significant association was detected regarding HDL level, QTc interval or heart size, and COVID-19 fatality odds.

Conclusion The present findings demonstrated that obesity, higher levels of CRP, blood sugar, D-dimer, and lipid markers were likely to be predictive factors of COVID-19-related mortality odds.

Keywords Blood sugar · Body weight · Cholesterol · COVID-19 · Inflammation · Thrombosis

Background

From the onset of the coronavirus disease 2019 (COVID-19) worldwide outbreak, approximately 41,570,883 patients have been diagnosed with the disorder. According to the WHO report, about 1,134,940 patients were reported to have died until October 23, 2020 (https://covid19.who.int/?gclid=CjwKCAjw_sn8BRBrEiwAnUGJDnToj4uxvzG9fm5s4201MBEj1NL0enL28io7p9SOSMh6-6PBVcegjRoCT_wQAvD_BwE).

A wide spectrum of COVID-19 manifestations has been recognized, from asymptomatic infection or mild symptoms in most subjects to severe deleterious respiratory infection in approximately one-fifth of the patients [1, 2].

Even though much research has been conducted on the COVID-19 patients' characteristics on admission and the factors affecting their hospitalization duration, mortality, and

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morbidity, there is no clearly defined risk factor. Advance ages (≥ 65 years), using immunosuppressive medications, smoking, having a history of type 2 diabetes mellitus, dyslipidemia, obesity or increased body weight (body mass index (BMI) ≥ 40 kg/m^2), cardiovascular disease (CVD), particularly hypertension (HTN), and ischemic heart diseases and renal disorders are among the most known risk factors for increasing the severity and death rates related to the novel RNA coronavirus (acute respiratory syndrome coronavirus 2 (SARS-CoV-2)) [1, 3–12].

Humoral and cellular immunity systems are activated after intracellular replication of the virus. Augmented inflammatory responses, as indicated by increased release of pro-inflammatory cytokines including interleukin (IL)-6, IL-10, and tumor necrosis factor (TNF)-α, and hyperstimulation of the immune system, which is known as "cytokine storm," occur then after. "Cytokine storm" could lead to acute respiratory distress syndrome (ARDS), massive bilateral viral pneumonia, hypercoagulation, stroke, pancreatic islets infection, cardiac, renal, or liver injury, and eventually multiple organ failure [4, 13]. Moreover, elevated angiotensin-converting enzyme 2 (ACE2) expression in the lower respiratory tract and increased contact of the virus with the cells via binding to ACE2 in the lungs could cause systemic infection. These events worsen the inflammatory state and activate immune responses that make the patients vulnerable to develop the more severe type of SARS-CoV-2 infection [2, 4].

Unfortunately, until the present, no definite treatment or vaccine has been recognized for SARS-CoV-2. Therefore, exploring the non-survived patients' characteristics compared to survived subjects and introducing the critical risk factors of COVID-19 mortality applying multivariable logistic regression would further our knowledge of this virulent disorder's treatment and enhance patients prognosis. In particular, such studies facilitate the early identification of most at-risk subjects for mortality in an emergency condition, monitoring these patients accurately and making therapy decisions and hospital discharge accordingly [1, 5]. However, due to the differences in demographic and genetic features of the various population, the generalizability of previous reported pathophysiological parameters to COVID-19 patients from all over the world may be limited. Besides, to our knowledge, the current evidence on characteristics of patients with COVID-19 in our region and their mortality risk does not seem to provide enough information and requires further evidence.

Therefore, the primary objective of the current study was to explore the differences in clinical and laboratory assessments of a sample of survived and non-survived patients with COVID-19 admitted to an academic referral hospital in Rasht, Iran. We also aimed to investigate the risk factors of COVID-19 mortality.

Methods

Participants

In the current single-center case-control study, we selected 250 adult COVID-19 patients aged older than 18 years who were admitted to Razi university hospital, the COVID-19 referral hospital in Rasht, Guilan, Northern Iran, from April 21 to August 21, 2020. The subjects younger than 18 years and those whose anthropometric or laboratory findings had not been recorded were not enrolled. Case group included 103 patients who were reported to dye due to COVID-19 (which are analyzed as non-survivors), and control group included 147 sex-matched patients who were discharges or recovered (which are analyzed as survivors).

Upon admission, the diagnosis of COVID-19 was performed according to WHO interim guidance and national protocols published by the Ministry of Health and Medical Education, Iran. Chest computed tomography (CT) scan results were used for determining abnormalities on chest CT imaging. Nasopharyngeal or oropharyngeal swab samples real-time reverse transcriptase-polymerase chain reaction (RT-PCR) test was applied for SARS-CoV-2 detection. The COVID-19 infection well-known or typical symptoms were also considered, including fever, cough, diarrhea, and respiratory symptoms (i.e., dyspnea, cough).

The patients or a member of their family were provided informed consent. Also, the research was performed based on the guidelines of the 2013 version of the Helsinki Declaration. It was approved by the review board of Cardiovascular Diseases Research Center, Department of Cardiology, Heshmat Hospital, School of Medicine (research number = 99012701), and Ethics Committee of Guilan University of Medical Sciences (ethical code number = IR.GUMS.REC.1399.017).

Procedures and outcomes

The information on demographic data (age and sex), underlying disorders, and past medical history (diabetes, HTN, previous CVD, coronary artery disease, or other conditions), the length of hospitalization, having gastrointestinal symptoms at admission, anthropometric measures (height and weight), and the clinical outcome (died or discharged alive) was extracted from the hospital electronic medical records. An experienced clinician reviewed and verified the data. A third researcher resolved the discrepancies in case of any differences in interpreting the data between the two primary reviewers.

After collecting blood samples within 48 h of admission, laboratory assessments were performed. Serum levels of C-reactive protein (CRP), was assessed using the immunoturbidimetric method according to the manufacture's guide (APTEC diagnostics NV, Belgium; Novin Biokit, Ref.

No. R130, Tehran, Iran). Besides, serum D-dimer concentration was investigated by applying an immunoturbidimetric assay (Diagnostica Stago, Asnières, France).

Fasting blood glucose (FBG) and total cholesterol (TC) levels were assessed by the enzymatic method using glucose oxidase and cholesterol esterase and cholesterol oxidase, respectively, applying commercial kits manufactured by MAN Co. (Tehran, Iran) and Auto-Analyzer (Hitachi, Japan) based on manufacturer's instructions. In terms of assessing triglyceride (TG), the same method was applied, but with glycerol phosphate oxidase using the commercial kit manufactured by Bionic Corporation and Auto-Analyzer (Hitachi, Japan). High-density lipoprotein (HDL) level was additionally evaluated based on enzymatic method (MAN Co., Tehran, Iran), and low-density lipoprotein (LDL) was estimated by Friedewald formula. Serum creatinine level was also investigated according to the manual instruction of the kit from MAN Co. (Tehran, Iran).

All commercial kits were confirmed by the Iran Health Reference Laboratory. All analyses were carried out in a certified clinical laboratory affiliated to Guilan University of medical sciences.

Electrocardiography (ECG) paper tracing recorded at 25 mm/s paper speed at 10 mm/mV gain setting was applied to determine the QT interval. The QT interval defined as the average interval between Q wave onset to the T wave end was evaluated using a single lead, representing the most prolonged QT with a prominent absence of U wave. Also, Bazett formulas (corrected QT interval (QTc) = QT/√ RR) was applied for modifying the evaluated QT interval (or QTc) for the effects of rate. The heart size defined as the transverse diameter of heart shadow (TDH) was estimated by applying chest posterior-anterior radiographs (PA chest X-ray). TDH was assessed via sketching a line near the heart shadow middle and the spine with a line from the heart's right border to the last line. A different line from the heart's left edge was drawn from the line in the heart shadow middle. The two lengths were summed up to calculate the TDH. Also, the ratio between the chest diameter and the heart widest portion that was estimated by drawing a line at the level of diaphragm right leaf to the inner border of the rib cage on the right and on the left was considered as the cardiothoracic ratio (CTR). A CTR was regarded as abnormal if it was > 1:2 (50%).

Statistical analysis

Normal distribution was assessed by the Shapiro-Wilk test. Between-group differences of skewed and normally distributed data were determined using the Mann-Whitney *U* test or independent sample *T* test, respectively. Continuous variables were reported as mean (standard deviation, SD) in normally distributed data or median (interquartile range, IQR) in case of data with skewed distribution. Chi-square or Fisher's exact test evaluated between-group differences of categorical variables, and the data were presented as proportions (%). To estimate the association between variables of interest and mortality, odds due to COVID-19 infection the logistic regression model was applied, and odds ratios (ORs) and 95% confidence intervals (95% CIs) were presented. Age, sex, length of hospitalization, and BMI levels [for analyzing laboratory data] were considered the second regression model (multivariable logistic regression analysis). Test for trend (*P* for trend) was carried out considering each quartile's median value as a continuous variable in the regression analysis. All analyses were performed applying IBM SPSS version 24 software (version 24.0; SPSS, Chicago, IL).

Results

Patient characteristics

A total of 250 hospitalized patients with confirmed COVID-19 with a mean (SD) age of 59.61 (16.55) years (of whom about 76 (30.4%) were < 50 years) were enrolled in the current analysis. About 124 (49.6%) >patients were women, and 126 (50.4%) were men. Overall, the mean duration of hospitalization was about 8.65 (5.49 days). Regarding the methods of SARS-CoV-2 infection diagnosis, 40 patients (16.0%) showed abnormal chest CT images, 169 (67.6%) had two RT-PCR assay positive findings, and 41 (46.4%) experienced severe clinical manifestation of upper respiratory symptoms upon admission. Overall, nearly 20% of the admitted subjects reported nausea, vomiting, and diarrhea, with vomiting as the most common on-admission gastrointestinal complaint.

The comparison of demographics and baseline features of included COVID-19 cases according to survival status is demonstrated in Table 1. Non-survived patients (n = 103) were considered as cases and survivors (n = 147) were included as sex-matched controls. The patients who died were significantly older than the discharged patients (mean age = 62.87 (16.74) vs. 57.33 (16.07) years, respectively; P value = 0.009). The proportion of the patients older than 50 years old tended to be higher among the non-survived group than the discharged patients (78 (75.7%) vs. 96 (65.3%), respectively), though no statistically significant differences were detected.

Concerning the history of comorbidities, there was a significant difference between the two studied groups. Overall, the proportion of non-survivors with any documented history of a medical condition (n = 89; 86.5%) was greater than that of survivors (n = 97; 65.1%) (P value = 0.011; Table 1). Having a history of HTN alone (n = 17 (16.5%)), HTN and diabetes (n = 15 (14.6%)) and coronary artery disease (n = 33 (32.1%)) were more prevalent among non-survivors, while having

Table 1 Comparison of baseline characteristics between two groups of enrolled patients

		Non-survived (n = 103)	Survived (n = 147)	P value
Sex (number (%))	Male	54 (52.4%)	70 (47.6%)	0.454
	Females	49 (47.6%)	77 (52.4%)	
Age (years) (mean (SD))		62.87 (16.74)	57.33 (16.07)	*0.009*
Age categories (number (%))	Less than 50 years old	25 (24.3%)	51 (34.7%)	0.078
	> 50 years old	78 (75.7%)	96 (65.3%)	
COVID-19 testing results (number (%))	Abnormal chest CT images	8 (7.8%)	32 (21.8%)	*0.021*
	RT-PCR test two positive results	76 (73.8%)	93 (63.3%)	
	Severe clinical manifestation of upper respiratory symptoms	19 (18.4%)	21 (14.3%)	
Length of hospitalization (days) (median (IQR))		7 (7)	7 (4)	0.766
Having gastrointestinal symptoms at admission (number (%))	Diarrhea	6 (5.8%)	11 (7.5%)	0.585
	Vomiting	15 (14.6%)	18 (12.2%)	
	Abdominal pain	1 (1.0%)	0 (0.0%)	
Past medical history (number (%))	Hypertension	17 (16.5%)	16 (10.9%)	*0.011*
	Diabetes	7 (6.8%)	13 (8.8%)	
	Hypertension and Diabetes	15 (14.6%)	15 (10.2%)	
	Coronary artery disease	33 (32.1%)	31 (21.1%)	
	Others	17 (16.5%)	22 (14.1%)	

The italic numbers indicate significant differences

SD standard deviation, *IQR* interquartile range, *CT* chest computed tomography, *RT-PCR* real-time reverse transcriptase-polymerase chain reaction

diabetes alone was nearly more prevalent among survived patients (n = 13 (8.8%)) (Table 1).

Upon-admission BMI and the clinical findings of the enrolled patients are presented in Table 2. Compared with the discharged patients, the subjects who died were more likely to be obese as evidenced by higher median BMI levels (median (IQR) = 27.68 (4.04) vs 25.71 (3.84) kg/m^2, P value = 0.01). Regarding on-admission serum biomarkers, non-survivor

Table 2 Comparison of anthropometric and laboratory values and cardiac function indicators between two groups of enrolled patients

	Non-survived (n = 103)	Survived (n = 147)	P value
Anthropometric indicator			
BMI (kg/m^2) (median (IQR))	27.68 (4.04)	25.71 (3.84)	*0.001*
Serum biomarkers			
CRP (mg/l) (median (IQR))	105.00 (143.00)	99.00 (62.00)	*0.016*
FBS (mg/dl) (median (IQR))	133.50 (158.50)	110.00 (45.00)	*0.000*
TC (mg/dl) (median (IQR))	132.00 (55.00)	123.00 (46.00)	*0.033*
TG (mg/dl) (median (IQR))	138.00 (83.00)	113.00 (71.00)	*0.001*
LDL (mg/dl) (median (IQR))	71.40 (43.00)	65.00 (34.00)	0.122
HDL (mg/dl) (median (IQR))	35.00 (19.00)	35.00 (13.00)	0.719
Creatinine (mg/dl) (median (IQR))	1.30 (1.10)	1.00 (1.31)	*0.005*
D-dimer (ng/ml) (median (IQR))	500.00 (400)	267.50 (636.75)	0.561
Cardiac function indicators			
QTc interval (ms) (mean (SD))	420.00 (53.00)	430.00 (60.00)	0.458
Heart Size (mm) (median (IQR))	126.25 (33.03)	120.23 (20.48)	0.103

The italic numbers indicate significant differences

IQR interquartile range, *SD* standard deviation, *BMI* body mass index, *CRP* C-reactive protein, *FBS* fasting blood sugar, *TC* total cholesterol, *TG* total triglyceride, *LDL* low-density lipoprotein-cholesterol, *HDL* high-density lipoprotein-cholesterol

patients were demonstrated to have less favorable levels of serum levels of inflammatory and glycaemia markers, lipid profile, and renal function marker, including higher levels of CRP (median (IQR) = 105.00 (143.00) vs. 99.00 (62.00) mg/l, *P* value = 0.016), FBS (median (IQR) = 133.50 (158.50) vs. 110.00 (45.00) mg/dl, *P* value < 0.001), TC (median (IQR) = 132.00 (55.00) vs. 123.00 (46.00) mg/dl, *P* value = 0.033), TG (median (IQR) = 138.00 (83.00) vs. 113.00 (71.00) mg/dl, *P* value = 0.001), and creatinine (median (IQR) = 1.30 (1.10) vs. 1.00 (1.31) mg/dl, *P* value = 0.005). However, there was no between-group difference in serum LDL and HDL levels. Furthermore, the two studied groups of patients exhibited similar findings on serum D-dimer levels and cardiac function biomarkers including QTc interval and heart size (Table 2).

Risk factors for COVID-19-related death

In order to further investigate the predictors of COVID-19-related mortality, the logistic regression model (crude and multivariable) was run and the results are presented in Table 3. According to the crude logistic regression analysis, anthropometric indices and serum biomarkers that were demonstrated to be positively associated with COVID-19-related death risk when comparing the highest quartile compared to the lowest were as follows: increased BMI (OR = 2.66; 95% CI = 1.27–5.58), and higher serum concentrations of CRP (OR = 2.52; 95% CI = 1.23–5.16), FBS (OR = 3.16; 95% CI = 1.52–6.56), TC (OR = 2.12; 95% CI = 1.03–4.36), TG (OR = 4.06; 95% CI = 1.90–8.68), creatinine (OR = 2.31; 95% CI = 1.12–4.76), and D-dimer (the 2nd and 3rd quartile compared to the lowest: OR = 0.11; 95% CI = 0.01–0.93; OR = 4.34; 95% CI = 1.85–10.19, respectively) (Table 3).

The multivariable logistic regression analysis adjusted for age, sex, length of hospitalization, and BMI levels [in terms of laboratory values], revealed similar results except for LDL, HDL, and creatinine serum levels in relation to COVID-19 mortality. It was found that compared to the lowest values, elevated BMI levels and higher levels of CRP increased the odds of COVID-19 fatality by about 2 times (OR = 2.49; 95% CI = 1.15–5.41; OR = 2.28; 95% CI = 1.08–4.78, respectively); increased FBS levels raised the COVID-19-related death odds by about 3-fold (OR = 2.88; 95% CI = 1.35–6.17); higher levels of TC and LDL elevated the odds of COVID-19 fatality by about 2 times (OR = 2.55; 95% CI = 1.19–5.45; OR = 2.27; 95% CI = 1.07–4.79, respectively); TG elevated the odds of COVID-19 mortality by approximately 2–5 times (the 2nd and 4th quartile compared to the lowest: OR = 2.51; 95% CI = 1.13–5.60; OR = 5.14; 95% CI = 2.28–11.56, respectively); raised levels of D-dimer also tended to increase the death odds due to COVID-19 by about 5-fold (the 3rd quartile compared to the lowest: OR = 5.68; 95% CI = 2.22–14.49). No significant association was detected regarding QTc interval or heart size and COVID-19 fatality odds neither in crude nor in multivariable regression. Although elevated serum HDL level was likely to be a protective factor against COVID-19-related mortality odds according to the crude regression model (the 3rd quartile compared to the lowest: OR = 0.47; 95% CI = 0.22–0.98), this association did not remain significant anymore in the multivariable regression model (Table 3).

Discussion

According to the findings of the current case-control study on Iranian patients with COVID-19, it was revealed that after considering the potential confounders and compared to the lowest values, elevated BMI levels and higher levels of CRP increased the odds of COVID-19 fatality by about two times; increased FBS levels raised the COVID-19-related death odds by about threefold; higher levels of lipid markers including TC and LDL elevated the odds of COVID-19 fatality by almost two times; TG elevated the odds of COVID-19 mortality by approximately 2–5 times; raised levels of D-dimer also tended to increase the death odds due to COVID-19 by about fivefold. However, we failed to find a significant association between HDL and creatinine serum levels, QTc interval or heart size, and COVID-19 fatality odds.

Obesity and COVID-19 mortality

Based on the current results, obesity, as indicated by elevated BMI levels, could be accompanied by increasing the mortality risk of COVID-19. In line with our findings, a retrospective cohort study was conducted by Simonnet et al. on the association between clinical features, such as BMI, and the need for invasive mechanical ventilation (IMV) in 124 hospitalized COVID-19 patients. It was indicated that having a BMI higher than 35 kg/m^2 was associated with about seven times increased need for in-hospital mechanical ventilation (OR: 7.36; 95% CI = 1.63–33.14) compared to normal-weight individuals with BMI of less than 25 kg/m^2 [14]. Likewise, in another retrospective study on 3615 COVID-19 patients younger than 60 years old, in comparison with those with a BMI of less than 30 kg/m^2, grade I of obese subjects (with a BMI of 30–34 kg/m^2) have been suggested to be at about 2 times greater risk of being admitted to both acute and critical care OR = 2.0 (95% CI = 1.6–2.6) and OR = 1.8 (95% CI = 1.2–2.7), respectively). Similarly, grade II of obese individuals (with a BMI of ≥ 35 kg/m^2) have been proposed to be at about 2 (OR = 2.2; 95% CI, 1.7–2.9) and 3.5 times (OR = 3.6; 95% CI = 2.5–5.3) greater risk of being admitted to acute and critical care, respectively [14, 15]. Similarly, another retrospective research on 280 COVID-19 cases reported that the patients who suffer from severe/critical symptoms had significantly higher BMI levels than the patients with mild and

Table 3 Odds ratio and 95% confidence interval for COVID-19-related death according to quartiles of anthropometric and laboratory values and cardiac function indicators

	Quartiles				*P* for trend
	1st quartile	2nd quartile	3rd quartile	4th quartile	
Anthropometric indicator					
BMI (kg/m^2)					
Survived/non-survived	43/19	42/21	34/30	28/33	
Median	22.43	25.39	27.66	30.12	
Crude model	1.00	1.132, 0.53–2.40	1.997, 0.96–4.14	*2.66, 1.27–5.58*	*0.003*
Multivariable adjusted model [a]	1.00	1.03, 0.47–2.23	1.751, 0.82–3.70	*2.49, 1.15–5.41*	*0.010*
Serum biomarkers					
CRP (mg/l)					
Survived/non-survived	41/24	37/25	44/17	25/37	
Median	46.00	87.00	115.00	183.00	
Crude model	1.00	1.15, 0.56–2.36	0.66, 0.31–1.40	*2.52, 1.23–5.16*	*0.012*
Multivariable adjusted model [b]	1.00	1.17, 0.56–2.47	0.61, 0.28–1.34	*2.28, 1.08–4.78*	*0.037*
FBS (mg/dl)					
Survived/non-survived	41/22	42/20	41/21	23/39	
Median	85.00	103.50	132.00	253.00	
Crude model	1.00	0.88, 0.42–1.86	0.95, 0.45–1.99	*3.16, 1.52–6.56*	*< 0.001*
Multivariable adjusted model [b]	1.00	0.73, 0.33–1.60	0.73, 0.33–1.61	*2.88, 1.35–6.17*	*< 0.001*
TC (mg/dl)					
Survived/non-survived	39/24	46/19	36/26	26/34	
Median	88.00	116.00	139.50	169.50	
Crude model	1.00	0.67, 0.32–1.40	1.17, 0.57–2.40	*2.12, 1.03–4.36*	*0.016*
Multivariable adjusted model [b]	1.00	0.68, 0.31–1.47	1.19, 0.56–2.53	*2.55, 1.19–5.45*	*0.006*
TG (mg/dl)					
Survived/non-survived	47/16	37/26	37/25	26/36	
Median	76.00	107.00	145.50	200.00	
Crude model	1.00	2.06, 0.96–4.40	1.98, 0.92–4.24	*4.06, 1.90–8.68*	*0.001*
Multivariable adjusted model [b]	1.00	*2.51, 1.13–5.60*	2.14, 0.96–4.75	*5.14, 2.28–11.56*	*0.000*
LDL (mg/dl)					
Survived/non-survived	38/25	43/20	39/23	27/35	
Median	36.80	59.00	76.20	99.80	
Crude model	1.00	0.70, 0.34–1.47	0.89, 0.436–1.84	1.97, 0.96–4.01	*0.044*
Multivariable adjusted model [b]	1.00	0.80, 0.37–1.72	0.99, 0.47–2.10	*2.27, 1.07–4.79*	*0.023*
HDL (mg/dl)					
Survived/non-survived	36/31	40/24	42/17	29/31	
Median	22.00	32.00	39.00	50.00	
Crude model	1.00	0.69, 0.34–1.40	*0.47, 0.22–0.98*	1.24, 0.61–2.49	0.727
Multivariable adjusted model [b]	1.00	0.81, 0.39–1.68	0.529, 0.245–1.14	1.44, 0.68–3.05	0.487
Creatinine (mg/dl)					
Survived/non-survived	44/21	47/23	27/27	29/32	
Median	.08	1.00	1.34	2.67	
Crude model	1.00	1.02, 0.49–2.10	2.09, 0.99–4.41	*2.31, 1.12–4.76*	*0.012*
Multivariable adjusted model [b]	1.00	0.86, 0.41–1.829	1.77, 0.81–3.84	1.62, 0.74–3.56	0.151
D-dimer (ng/ml)					
Survived/non-survived	41/22	16/1	12/28	31/8	
Median	200.00	261.00	518.00	1231.00	
Crude model	1.00	*0.11, 0.01–0.93*	*4.34, 1.85–10.19*	0.48, 0.18–1.22	0.266

Table 3 (continued)

	Quartiles				*P* for trend
	1st quartile	2nd quartile	3rd quartile	4th quartile	
Multivariable adjusted model [b]	1.00	0.15, 0.01–1.32	*5.68, 2.22–14.49*	0.62, 0.23–1.66	0.532
Cardiac function indicators					
QTc interval (msec)					
Survived/non-survived	36/26	33/29	37/23	37/24	
Median	386.00	411.50	440.00	460.00	
Crude model	1.00	1.21, 0.59–2.47	0.86, 0.41–1.77	0.89, 0.437–1.84	0.552
Multivariable adjusted model [b]	1.00	1.25, 0.59–2.62	0.93, 0.44–1.97	0.92, 0.44–1.93	0.649
Heart size (mm)					
Survived/non-survived	17/11	19/8	17/11	11/16	
Median	106.74	118.25	129.22	147.25	
Crude model	1.00	0.65, 0.21–1.99	1.00, 0.34–2.92	2.24, 0.76–6.61	0.078
Multivariable adjusted model [b]	1.00	0.79, 0.24–2.58	1.00, 0.33–3.02	1.79, 0.57–5.57	0.253

The italic numbers indicate significant differences

[a] Adjusted for sex, age, and length of hospitalization

[b] Adjusted for sex, age, length of hospitalization, and BMI

BMI body mass index, *CRP* C-reactive protein, *FBS* fasting blood, *TC* total cholesterol, *T* total triglyceride, *LDL* low-density lipoprotein-cholesterol, *HDL* high-density lipoprotein-cholesterol

moderate symptoms (25.8 vs. 23.6, respectively). They also showed that BMI was a risk factor for increased severity of SARS-CoV-2 (OR = 1.30; 95% CI = 1.09–1.54) [16].

Multiple mechanistic pathways may explain the adverse effects of obesity on death due to COVID-19. The concentrations of leptin (as a pro-inflammatory adipokine), oxidative stress and pro-inflammatory cytokines (i.e., IL-6, TNF-α, and CRP) have been shown to be higher among obese individuals. It is noteworthy that leptin is thought to be a certain modifier of maturation, development, and activity of B cells. On the other hand, the concentration of adiponectin (as anti-inflammatory adipokine) is reported to be lower in these patients. The imbalances in the mentioned factors could cause dysregulation of immune cells function that in turn may affect the viral infection progression. Besides, both obese patients and COVID-19 cases have an increased risk of hypercoagulation and thrombosis [2, 17–19].

Glycaemia and COVID-19 mortality

The majority of prior research has focused on the association between having diabetes history instead of blood sugar levels and COVID-19 fatality risk. Therefore, almost similar to our findings, some research and review articles found a negative association between hyperglycemia, weak glycemic control, and diabetes with COVID-19 fatality [3, 7, 12, 20–25]. As such, a recent systematic review recommended that health care providers consider monitoring blood glucose levels to be lower than 180 mg/dl (without triggering hypoglycemia) in most diabetic patients who have COVID-19 [7]. In a recent population-based cohort study by Holman et al., it was reported that COVID-19 in-hospital death odds ratios among type 1 and type 2 diabetic patients were 3.51 (95% CI = 3.16–3.90), and 2.03 (95% CI = 1.97–2.09), respectively, in comparison with those who had no diabetes. However, because of data limitation, the confounding variables were not considered in their regression analysis [3]. Likewise, Ciardullo et al. [26] observed having pre-existing diabetes was linked to an increased risk of COVID-19-related hospital death (RR = 1.56; 95% CI = 1.05–2.02) through a retrospective study performed in Italy on 373 COVID-19 hospitalized patients [26]. In a similar way, a systematic review and meta-analysis [20] on 83 observational studies of 78,874 hospitalized COVID-19 pointed out that the risk of suffering severe/critical COVID-19 infection and its related in-hospital fatality increased by about 2-fold (OR = 2.10, 95% CI 1.71–2.57) and 2.7-fold (OR = 2.68, 95% CI = 2.09–3.44), respectively, in the case of having pre-existing diabetes [20]. Likewise, another meta-analysis on six studies (included 1558 COVID-19 subjects) diabetes was introduced as a risk factor (OR = 2.47; 95% CI = 1.67–3.66) for COVID-19 infection [21]. Similarly, another more extensive meta-analysis ($n = 30$ studies with 6452 patients) reported subjects with diabetes were shown to have elevated risk of both severe types of COVID-19 (RR = 2.45; 1.79, 3.35), its complications including ARDS (RR = 4.64; 1.86, 11.58) disease progression (RR = 2.38; 1.88, 3.03) and its related death (RR = 2.12; 1.44, 3.11). However, the study did not find a significant association between diabetes and COVID-19 patients' ICU admission [23].

Thus, having a history of diabetes mellitus, insulin resistance, and chronic hyperglycemia render the COVID-19-infected patients more susceptible to developing severe infection types, probably through metabolic disruption, triggering a pro-inflammatory state and oxidative stress in addition to immunosuppression [9]. Increased blood sugar may also link to deterioration in T cell responses, disruption in immune function, and cytokine release. Moreover, those with diabetes might exert modified microenvironment and higher expression of ACE-2, elevated platelet aggregation, hypercoagulation, and thrombosis, increasing the likelihood of viral uptake, infection progression, "cytokine storm," and severe COVID-19 outcomes. Diabetics are also at elevated risk of endothelial dysfunction, cardiovascular and renal complications, and peripheral neuropathy. Hence, this may have an additive effect of being more susceptible to COVID-19 complications (i.e., ARDS, intensive care unit admission, and mechanical ventilation), severe COVID-19, and death. On the other hand, COVID-19 intensifies the complications and prognosis of diabetes, such as diabetic ketoacidosis. However, it is not well-understood whether blood sugar directly affects SARS-CoV-2 infection progression or the virus changes carbohydrates' metabolism [9, 12, 13, 20, 26].

The inflammatory marker and COVID-19 mortality

Consistent with our findings, a recent study by Wang L. demonstrated that patients with moderate SARS-CoV-2 infection had higher CRP concentrations than mild patients. Also, the patients had greater CRP levels than those in the moderate. Similarly, the critical patients' group had greater CRP levels compared to severe patients. Besides, as the infection progressed, the serum levels of CRP and the largest lung lesion diameter get raised. Interestingly, they also suggested a significant positive correlation between serum levels of CRP and the diameter of lung lesions as well as severe manifestations of the disease (correlation coefficient = 0.873, 0.734) [27]. Additionally, in a retrospective cohort study comprised of 2957 hospitalized Iranian COVID-19 cases (2656 were cured, and 301 died), consistent with our findings, it was demonstrated that cured or discharged subjects had significantly lower serum CRP levels (median = 16 mg/l) than the patients who died (median = 45 mg/l). Also, after considering confounding factors including sex, age, and laboratory values in the multivariable model, it was revealed that CRP levels raised the risk of death from SARS-CoV-2 infection among those who had diabetes with or without other comorbidities (n = 267) (OR = 1.02; 95% = 1.0–1.04), or CVDs with or without other comorbidities (n = 168) (OR = 1.09; 95% CI = 1.04–1.14) [12]. The positive correlation between disease severity and serum CRP concentrations and the value of this inflammatory marker as a predictor of CIVID-19 progression and its complications, including respiratory failure and requiring ventilator support, have additionally been confirmed in further studies [26, 28–31]. A systematic review and meta-analysis on 16 studies, including 1896 survivors and 849 non-survivors COVID-19 cases, documented that serum levels of CRP of non-survivor patients was significantly greater than the survivors (standard difference in means = 1.371) [30]. A retrospective cohort study of 176 patients with COVID-19 showed partially similar results to the present findings [32]. Although no significant differences in serum CRP levels of COVID-19 survivors and non-survivors were found on admission, on day 7, a greater mean CRP was related to elevated mortality. Furthermore, mean CRP levels were significantly higher in the groups of patients needing critical care than those with the less progressed disorder at admission and on day 7. Although, in contrast to our results, the researchers failed to find a significant relationship between on-admission CRP levels and the odds of mortality, increased levels of this factor (> 101 mg/dl) on day 7 was associated with elevated COVID-19 mortality risk (OR = 3.7; 95% CI = 1.1–12.5) than the patients with < 100 mg/dl CRP levels after adjusting for comorbidities at baseline and medications consumption [32].

In pulmonary disorders with pro-inflammatory properties, serum CRP level usually increases as a result of elevated inflammatory factors such as IL-6, IL-1, or TNF-α [27, 28]. On the other hand, it has been well-known that excessive inflammatory responses may be primarily involved in SARS-CoV-2-related organ damage and infection progression [27, 28]. Hence, it can be proposed that elevated CRP levels may represent a marker for augmented inflammatory state, and disease severity in the early stage of SARS-CoV-2 infection, particularly among non-survivors of the cases with severe/critical COVID-19. Due to the prompt elevation in CRP production by the initiation of an inflammatory state in the body, cell damage, or injury of the tissues, this acute phase reactant level may also contribute to the stimulation of the complement function and enhancement of phagocytosis [27, 28]. Hence, since elevated CRP levels may indicate response to inflammation, and host defense systems function, its upon-admission levels should be considered an important biomarker of disease progression/death risk due to COVID-19.

Creatinine and COVID-19 mortality

In contrast to previous studies results [12, 33] and the present crude regression model, we failed to detect a statistically significant relationship between upon-admission serum creatinine level and COVID-19-related death odds. There was only a significant difference between the non-survived and survived patients concerning creatinine concentration in serum.

In a recently published prospective cohort study on 701 hospitalized COVID-19 cases, it was proposed that after considering confounding factors including age, gender, the severity of the disease, comorbidities, and leukocyte count in the

COX regression models, raised baseline serum creatinine (hazard ratio: 2.10, 95% CI: 1.36–3.26), and increased baseline blood urea nitrogen (3.97, 2.57–6.14) were accompanied by an increased risk of COVID-19-related in-hospital fatality risk [33]. Furthermore, in a retrospective cohort study described earlier, similarly with our results, it was demonstrated that cured or discharged subjects had significantly lower creatinine serum levels (median = 1.00 mg/dl) than the patients who died (median = 1.20 mg/dl). However, contrary to the current findings, it was reported that creatinine levels elevated SARS-CoV-2-related mortality risk among those who had diabetes with or without other comorbidities (n = 267) (OR = 12.72; 95% = 1.87–86.70) after considering confounding factors including sex, age, and laboratory values in the multivariable model [12]. It is of note that augmented pro-inflammatory factors and disturbed immune cells function as consequences of abnormal kidney function and increased creatinine levels may render the patients at a greater risk of COVID-19 [34].

The thrombosis biomarker and COVID-19 mortality

Although the information on D-dimer levels was available for 59 patients in case group and 100 patients in control group, our findings suggested those with increased levels of this biomarker (median=518.00 ng/mL) compared to those who had a median of 200.00 ng/mL are about five times more likely to die due to COVID-19. The current findings further confirmed previous evidence that suggested increased levels of D-dimer could be associated with high severity and death risk due to COVID-19, nearly always concurrent with augmented levels of pro-inflammatory factors (i.e., ferritin, lactate dehydrogenase, troponin I and TNF-α, IL-1b, and IL-6) [35]. In accordance with our results, the results of a recent systematic review of 6 articles on 1355 hospitalized subjects with moderate to severe COVID-19 (of which 391 were non-survivors and 964 were survivors) showed D-dimer levels are more likely to be greater in non-survivors compared to the survivors (SMD = 3.59 ng/l; 95% CI 2.79–4.40 ng/l) [35]. Also, in line with these results, in retrospective research on 248 COVID-19 cases, it was reported that the median D-dimer level of non-survivors (n = 17; 6.21 mg/l) was significantly greater than that of survivors (n = 231; 1.02 mg/l). Multivariable regression revealed that on admission, D-dimer higher than 2.0 mg/l was related to higher odds of mortality (OR = 10.17; 95% = CI 1.10–94.38). Furthermore, the D-dimer level was also shown to be significantly elevated by increasing COVID-19 severity [36]. Likewise, Tang et al. [37] showed a group of COVID-19 survivors (n = 162) had a significantly lower D-dimer level (0.61 μg/ml) compared the non-survivors patients (n = 21) (2.12 μg/ml). Similarly, Gao and cols reported that a group of patients with critical COVID-19 infection had significantly lower levels of the mild group (median level = 0.21 μg/l) compared to those in the severe group (median level = 0.49 μg/l). Besides, a higher D-dimer level (> 0.28 μg/l) was accompanied by an increased risk of severe COVID-19 in comparison with those who had a lower level (≤ 0.28 μg/l) (OR = 12.139; 95% CI = 1.716, 85.86) [38]. Another study investigated the variation of the D-dimer level through 10 days. Improved and poor patients were reported to have higher on-admission D-dimer concentration than those in the ordinary group with ORs of 1.42 (95% CI = 1.04–1.96) and 1.35 (95% CI: 1.02–1.80), respectively. While the level remained raised in the poor group by disease progression, it constantly reduced among the improved group [39]. Similarly, another group of researchers aimed to assess the D-dimer levels dynamic changes and risk for venous thromboembolism (VTE) throughout the infection's progression through a study on 57 COVID-19 patients with pneumonia and 46 patients suffering from community-acquired bacterial pneumonia (CAP). They observed that D-dimer levels were significantly elevated at admission in both groups of studied patients though COVID-19 patients had significantly higher levels of this biomarker than the CAP patients. Also, it was found that there was a significant correlation between D-dimer and inflammation indicators including hs-CRP (R = 0.426) among the patients with COVID-19. Interestingly, D-dimer levels concurrent with hs-CRP levels were likely to be lower after treatments in majority of patients with acceptable clinical prognosis [40]. Moreover, in contrast to our study, no significant difference in the mean levels of D-dimer of survivors and non-survivors neither on day 1 nor on day 7 of hospitalization was detected in a retrospective cohort study [32] which is described earlier. They showed that mean levels of this factor was related to a raised need for critical care on day 7. Although there was not any significant association between D-dimer levels at admission and mortality odds due to COVID-19, increased level of this biomarker (higher than 501 ng/ml) was shown to be related to a decreased mortality odds on and day 7 of hospitalization compared to the patients with D-dimer levels < 500 ng/ml (OR = 11.9; 95% CI = 1.2–109.9) [32].

The available evidence provided an extensive account of a relationship between pre-existing CVDs, the common comorbid disorders with COVID-19, and SARS-CoV-2 pathology. It has been found that even asymptomatic or mildly symptomatic COVID-19 subjects may manifest cardiovascular abnormalities including myocardial inflammation, hyperthrombosis, and hypercoagulation, even after recuperation from the infection [41, 42]. On the other hand, hypercoagulation may contribute to the pathogenesis of severe COVID-19 infection progression, probably due to persistently raised production of pro-inflammatory cytokines release following virus invasion. Besides, increased secretion of pro-inflammatory factors may raise the expression of tissue factor (TF) on the endothelial cells and monocytes, leading to

stimulating a procoagulant activity. Additionally, thrombosis of the pulmonary vasculature might also occur because of the severe hypoxia as a certain stimulant of coagulation associated with an elevated risk of VTE. Hence, as a biomarker for coagulation, probably thrombosis, and pulmonary thromboembolism, D-dimer levels were widely investigated related to COVID-19 mortality risk [35, 36, 40, 43, 44]. Thus, as shown in our study, elevated D-dimer and CRP levels may serve as indicators of a severe pro-inflammatory state accompanied by a secondary hypercoagulation in COVID-19 cases [35, 36, 40, 43, 44].

Lipid profile and COVID-19 mortality

Like the present findings, a retrospective, observational cohort study on 3988 COVID-19 critically ill patients admitted to ICU reported that those who had hypercholesterolemia were at a higher risk of death due to viral infection normocholesterolemic patients (HR = 1.25; 95% CI = 1.02–1.52) [45]. Our current findings, which demonstrate serum levels of TC and TG could be robust predictors of COVID-19-related death, are partly in line with several previous researches [45, 46]. However, the negative association between serum LDL and COVID-19 fatality risk somewhat contradicted the earlier findings [46–49]. We failed to detect any significant relationship between serum HDL levels and COVID-19-related death risk, which refuted previous results that highlighted a protective role for this factor against COVID-19 mortality risk or severity [49, 50]. Partly in contrast to the present results, through a retrospective analysis, 228 COVID-19 cases were shown to have significantly lower serum concentrations of TG (median = 1.08 vs 1.21 mmol/l), HDL (median = 0.78 vs 1.37 mmol/l), LDL (median = 2.63 vs 2.83 mmol/l), and TC (median = 3.76 vs 4.65 mmol/l) compared to 1140 healthy age and sex-matched individuals [50]. In a similar way to this article and unlike our findings, mean serum levels of TC (126 mg/dl), LDL (69.5 mg/dl), and HDL (29.9 mg/dl) of 102 COVID-19 cases were reported to be lower than that of the healthy control group (mean levels of TG: 157.7 mg/dl, LDL: 100.6 mg/dl and 41.43 mg/dl, respectively). However, higher mean TG levels observed (155.4 mg/dl) COVID-19 cases in comparison with healthy individuals (115 mg/dl) were partly similar to those obtained in the current research [46]. When the researchers compared COVID-19 cases according to disease severity, the LDL level was lower among critical than non-critical patients (median = 50 mg/dl vs LDL: 69 mg/dl). LDL level less than 48 mg/dl was also suggested to be a risk factor of critical COVID-19 (OR = 2.07; 95% IC = 1.18–3.63); Additionally, nearly similar to our results, this study researchers demonstrated that median TG levels (145 mg/dl) of patients with critical COVID-19 infection were greater than median TG of in no-critical cases (138 mg/dl) [46].

Collectively, the abnormal lipid profile in COVID-19 cases may result from the increased inflammatory responses or "cytokine storm" and its associated immune dysfunction as well as disturbed lipid metabolism due to viral infection. In this regard and considering the role of eicosanoid increment and hypercoagulation in COVID-19 pathogenesis, many recent pieces of research have focused on prescribing omega-3 fatty acids+ aspirin due to the anticoagulant features of these agents and reducing eicosanoids [47, 51]. Moreover, since increased levels of TC, TG, and LDL are notable risk factors of CVDs, including HTN, considering the increased prevalence of these chronic disorders among SARS-CoV-2-infected patients, this issue may further explain the predictive role of these lipid markers in the COVID-19 case fatality. Besides, it has been indicated that tissue cholesterol concentration may contribute to the enhancement of ACE2 localization with viral entry into the cells and hence might affect COVID19 severity [52]. However, due to inconsistencies in literature reports, more well-designed cohort and experimental studies are required to fully determine the effects of lipid profile on COVID-19-related death and its progression [47, 51].

Cardiac function indicators and COVID-19 mortality

Based on the current findings, we failed to detect any significant association regarding QTc interval or heart size and COVID-19 fatality odds neither in crude nor in multivariable regression. This may be due to the low accuracy of left ventricular size recorded by chest X-ray in diagnosing COVID-19 myocarditis, a condition that has been proven to be accompanied by an increased risk of mortality due to this viral infection [53, 54]. Therefore, according to the present results, it can be hypothesized that the estimation of heart size using a chest X-ray may not be a reliable way for COVID-19-associated myocarditis and mortality risk assessment. Hence, other imaging modalities, including echocardiography and cardiac magnetic resonance (CMR), could be recommended. However, it should be noted that only 46 patients in case group and 64 patients in control group had PA chest X-ray results. Thus, due to the lack of data on heart size for majority of included patients, these results should be interpreted with caution.

Comorbidities and COVID-19

Based on the present results, the prevalence of elevated BMI and obesity, HTN, and diabetes, in addition to coronary artery diseases, were likely to be higher among non-survived compared to survived patients. These findings corroborate the previous reports highlighting these chronic diseases as risk factors for COVID-19 severity or death [11, 12, 16, 21, 24–26, 42]. Considering the strong relationship between comorbidities and COVID-19 high mortality rate, tissue damage, and functional status of different organs, patients' past medical

history should be tightly controlled in these patients. Hence the clinical data related to comorbidities must be considered in drafting the treatment and monitoring guidelines of COVID-19 subjects [1, 5].

Study limitation

The present study was subject to a few limitations that should be mentioned. First, the study's cross-sectional design might increase the risk of bias in data collection and impose some limits. Moreover, since the non-survived group included only subjects who died in a hospital, whereas at-home deaths that may occur following a long time after discharge were not considered in the analysis, the conclusions drew by the study should be interpreted with caution. Therefore, although the present findings are still useful as evidence for the factors related to mortality risk due to this novel coronavirus, large cohort studies will be needed to confirm the current findings.

Conclusion

In conclusion, the present findings demonstrated that higher levels of the inflammatory marker, CRP, blood sugar, D-dimer, and lipid markers' levels except for HDL level were likely to be independent predictive factors of COVID-19-related mortality odds regardless of the patient's age, sex, length of hospitalization, and BMI. Also, obesity increased the odds of mortality due to this novel coronavirus. Furthermore, patients who died due to COVID-19 infection had a higher history of chronic disorders, remarkably HTN, diabetes, and coronary artery disease than survived patients. These findings are a source of concern and highlight the need for precise evaluation of BMI, and serum biomarkers, including CRP, FBS, D-dimer, TC, TG, and LDL at triage and monitoring during hospitalization. Assessment of these factors could also be beneficial in the early detection of the most vulnerable patients who are at the highest risk of COVID-19 death, assigning the available limited care resources to them, and planning the most suitable treatment strategy.

Therefore, clinicians and health care providers should consider obesity and cardiovascular risk factors as serious risk factors for COVID-19 severe outcomes. Hence, these patients should receive careful observation, an appropriate therapeutic approach, and tight monitoring. Also, a healthy dietary strategy with regular physical activity may assist the patients to get proper therapeutic responses faster as these approaches attenuate pro-inflammatory state and modify the immune function, thus protect against viral infection progression and even reinforcement of response to vaccine administration.

However, extensive prospective cohort studies are required to validate the prognostic values of the present detected risk factors of COVID-19 death.

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Zeinab Ghorbani: Statistical analysis, data interpretation, writing—original draft

Seyede Sahere Mortazavi, Mona Naghshbandi, Farsima Faraghnia, and Zahra Ahmadnia: Data collection, data interpretation

All authors approved the final version and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Compliance with ethical standards

Competing interests The authors declare that they have no competing interests.

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