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Age-Adjusted in-Hospital Mortality in Patients with COVID-19 Infection: Impact of the Presence of Multiple Comorbidities

Nader Tavakoli[1], Nahid Hashemi-Madani[2], Mojtaba Malek[3], Zahra Emami[2], Alireza Khajavi[4], Rokhsareh Aghili[2], Maryam Honardoost[2], Fereshteh Abdolmaleki[2], Mohammad E. Khamseh[2*]

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Abstract

Background: Mortality has been indicated to be high in patients with underlying diseases. This study aimed to examine the comorbidities is associated with a higher risk of death during the hospital course.

Methods: We retrospectively evaluated the risk of in-hospital death in 1368 patients with COVID-19 admitted to 5 academic hospitals in Tehran between February 20 and June 13, 2020. We also assessed the composite end-point of intensive care unit admission, invasive ventilation, and death. The Cox proportional survival model determined the potential comorbidities associated with deaths and serious outcomes.

Results: The retrospective follow-up of patients with COVID-19 over 5 months indicated 280 in-hospital deaths. Patients with diabetes (risk ratio (RR), 1.47 (95% CI, 1.10-1.95); $P = 0.008$) and chronic kidney disease (RR, 1.72 (95% CI, 1.16-2.56); $P = 0.007$) showed higher in-hospital mortality. Upon stratifying data by age, patients aged <65 years showed a greater risk of in-hospital death in the presence of 2 (hazard ratio (HR), 2.68 (95% CI, 1.46-4.95); $P = 0.002$) or more (HR, 3.47 (95% CI, 1.69-7.12); $P = 0.001$) comorbidities, compared with those aged ≥ 65 years.

Conclusion: Having ≥ 2 comorbidities in nonelderly patients is associated with a greater risk of death during hospitalization. To reduce the mortality of COVID-19 infection, younger patients with underlying diseases should be the focus of attention for prevention strategies.

Keywords: COVID-19, Comorbidity, Invasive Ventilation, Mortality, Iran

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Introduction

The novel coronavirus SARS-CoV-2, presenting with heterogeneous clinical manifestations (1-3), easily predisposes susceptible patients to respiratory failure and death (1, 4, 5). Previous studies have demonstrated such underlying chronic diseases as diabetes mellitus (DM), hypertension (HTN), cardiovascular disease, and chronic obstructive pulmonary disease (COPD) are more likely to complicate the clinical course of coronavirus disease 2019 (COVID-19) (6, 7). The affected patients are at a greater risk of developing respiratory failure, being admitted to an intensive care unit (ICU), and eventually death (3, 8, 9). A study of 16061 patients in Yazd (Iran) showed that age and some underlying diseases increase the odds of death (10).

Corresponding author: Dr Mohammad E. Khamseh, khamseh.m@iums.ac.ir

1. Trauma and Injury Research Center, Iran University of Medical Sciences, Tehran, Iran
2. Endocrine Research Center, Institute of Endocrinology and Metabolism, Iran University of Medical Sciences, Tehran, Iran
3. Research Center for Prevention of Cardiovascular Disease, Institute of Endocrinology and Metabolism, Iran University of Medical Sciences, Tehran, Iran
4. Student Research Committee, Faculty of Paramedical Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran

↑What is "already known" in this topic:
Several studies demonstrated that comorbidities are associated with an increased risk of mortality in patients with coronavirus disease 2019 (COVID-19) infection.

→What this article adds:
This study indicated that having ≥2 comorbidities is associated with a higher risk of COVID-19 mortality in patients <65 years old.

Another study demonstrated DM, HTN, and obesity as the predictors of mortality in patients with COVID-19 (11). However, there are meaningful variations in population demographics, smoking rates, and popularity of comorbidities among the countries (12, 13). Therefore, comprehensive reports on the early clinical outcomes of COVID-19 from patients with varying ethnic backgrounds appear to be essential for identifying the subpopulations that have lower predictive power. This study aimed to evaluate the early clinical course of patients with COVID-19 hospitalized at various academic centers in Tehran, classified by the number and type of comorbidities.

Methods

Data Source and Data Collection

This retrospective cohort study was conducted at 5 academic hospitals (Firouzabadi, Firouzgar, Haftetir, Rasouleakram, and Yaftabad) affiliated with Iran University of Medical Sciences (IUMS) in Iran. These are public general hospitals actively involved during the COVID-19 pandemic. The study was approved by the ethics committee of the IUMS (ethic code: IR.IUMS.REC.1399.066). The necessity for informed consent was removed regarding the minimal-risk research using data collected in ordinary clinical practice. We registered all hospitalized patients with verified COVID-19 admitted between February 20, 2020, and June 13, 2020. Those with a positive polymerase chain reaction test result from a nasopharyngeal specimen were deemed to have COVID-19. Those without laboratory reports for COVID-19 who showed the clinical indications of COVID-19 along with typical chest computed tomography (CT) findings were also regarded as having COVID-19. For patients with a readmission through the study period, data from the first admission are conferred.

Medical certificates of all confirmed patients involving demographic data, baseline comorbidities, chest CT findings, smoking status, vital signs at the time of admission, along with hospital course data containing treatment with invasive mechanical ventilation, admission to ICU, duration of hospitalization, and patient situation at the time of discharge (alive or dead) were gathered. Comorbidities were identified by history and related medication. Data were extracted from patients' hospital documents during admission. All clinical profiles from 5 academic hospitals were centrally combined. The data were entered into a computerized database for further double-checking of all cases by some experienced technicians.

Comorbidities were defined based on patients' self-reports on admission. A total of 8 comorbidities, namely HTN, DM, chronic kidney disease (CKD), coronary artery disease (CAD), lung diseases, including asthma and COPD, cerebrovascular accidents (CVA), heart failure (HF), and malignancy consisted of the final analysis. Comorbidities were first recognized as a categorical variable (yes versus no) and subsequently ordered according to the number (single versus multiple).

Treatment with invasive mechanical ventilation, ICU admission, and death were the initial consequences of this study, calculated independently and as a complex reaction. All clinical outcomes are performed for patients who finished their hospital course (discharged alive or dead).

Statistical Analysis

The categorical variables are presented as numbers and percentages, while the continuous variables are represented as the median and interquartile ranges (IQR). To determine the effect of each of the 8 considered comorbidities on the incidence of either of the response variables, namely ICU admission, death, the composite outcome, and invasive mechanical ventilation, the arranged risk ratios were measured, employing the method proposed by Norton et al (2013), adapted for sex, age, duration of hospitalization, and the other comorbidities (14).

Finally, a survival analysis was accomplished to determine the death probability from the hospital admission date. For this purpose, the Kaplan-Meyer survival curve was distinctly for the patients with 0, 1, 2, or ≥ 3 comorbidities, and the Log-rank test evaluated the difference between these categories. Then, the Cox proportional hazard survival models were adjusted at the time of hospitalization to get the hazard ratios of death between those with and without any of the 8 discussed comorbidities. These models were regulated for sex, age, and other comorbidities. Statistical analyses were operated by applying Stata software Version 13. The significant level was set at $P < 0.05$.

Results

Baseline Characteristics and Comorbidities

This multicenter retrospective cohort study comprised 1368 (59.9% men) hospitalized COVID-19 patients with a median age of 58 years (IQR, 43-70). Comorbidity was registered for 1235 patients, of whom 633 (51.3%) reported having at least 1 comorbidity—26.6% one comorbidity, 15.1% two comorbidities, and 9.6% more than 2 comorbidities. The popularity of special comorbidities was as follows: DM (n = 362; 26.5%), HTN (n = 359; 26.2%), CAD (n = 99; 7.2%), HF (n = 44; 3.2%), CVA (n = 40; 2.9%), CKD (n = 67; 43, 3.1%), chronic liver disease (n = 14; 1%), Tuberculosis (TB) (n = 9; 0.7%), and human immunodeficiency virus (HIV) (n = 3; 0.2%). Baseline and clinical characteristics of the hospitalized patients as age, sex, opium addiction, smoking status, along with respiratory rate, systolic and diastolic blood pressure, temperature, and the presence of abnormal chest CT findings at the time of admission, classified based on type of comorbidity, are presented in Table 1.

Outcomes During the Hospital Course

Of the 1368 hospitalized patients, 414 (33%) patients were accepted to the ICU, 237 (18%) took invasive mechanical ventilation, and finally, 280 (20.6%) patients died through the hospital course. The results stratified by the presence or absence of any comorbidity are reported in Supplementary Figure 1. Compared with the patients without any comorbidity, those who recorded at least 1 comorbidity were more likely to be admitted to the ICU (48.3% vs 19%), get invasive mechanical ventilation (23.8% vs 14.2%), and die (30.2% vs 12.6%).

Table 1. Baseline and clinical characteristics of patients hospitalized with COVID-19 classified by various kinds of comorbidities

Variable	DM n=362	HTN n=359	CAD n=99	HF n=44	CVA n=40	CKD n=67	Malignancy n=37	Lung disease n=78	No comorbidity n=602
Sex (Male)	205/362 (56.6)	194 /359 (54.0)	61 /99 (61.6)	26 /44 (59.1)	25 /40 (62.5)	37 /67 (55.2)	21 /37 (56.8)	50/78 (64.1)	362/602(60.1)
Age (yrs)	65 (56-74)	69 (60-78)	70 (60-77)	75 (65-81)	70 (61-75)	68 (55-77)	65 (57-76)	64 (53-72)	49 (38-62)
Smoking									
No/unknown	283/297 (95.3)	276/289 (95.5)	74/82 (90.2)	36 /36 (100)	32/36 (88.9)	47/49 (95.9)	34 /36 (94.4)	49 /49 (86.0)	585/595 (98.3)
Former/current	14/297 (4.7)	13/289 (4.5)	8/82 (9.8)	0 /36 (0.0)	4 /36 (11.1)	2 /49 (4.1)	2/36 (5.6)	8/49 (14.0)	10/595(1.7)
Opium addiction (yes)	8/253 (3.2)	9 /237 (3.8)	4 /62 (6.5)	0/25 (0.0)	1 /16 (6.3)	2 /38 (5.3)	1/20 (5.0)	3 /45 (6.7)	6/591 (1.0)
T on admission	37 (36.8-37.5)	37 (37-37.5)	37 (36.9-37.5)	37.1 (36.8-37.5)	37 (36.9-37.5)	37 (36.8-37.5)	37 (36.9-37.7)	37.2 (37-37.6)	37.1 (36.9-37.5)
RR on admission	18 (17-20)	18 (17-20)	18 (17-20)	18 (16-20)	18 (17-22)	18 (16-20)	18 (18-21)	18 (17-20)	18 (16-20)
SBP on admission	120 (110-130)	120 (114-130)	120 (110-130)	123 (115-135)	135 (120-148)	120 (110-130)	111 (101-128)	120 (112-130)	120 (110-124)
DBP on admission	75 (70-80)	80 (70-80)	79 (70-80)	80 (70-84)	80 (70-85)	76 (68-80)	70 (60-80)	80 (70-85)	80 (70-80)
Abnormal chest CT(yes)	279/287 (97.2)	280/287 (97.6)	69 /74 (93.2)	28 /29 (96.6)	34 /36 (94.4)	45/48 (93.8)	28/29 (96.6)	61 /63 (96.8)	396/435 (91.0)

Data are presented as median (IQR), or n/N (%); N is the total number of patients with available data. DM; Diabetes mellitus, HTN; Hypertension, CAD; Coronary artery disease, HF; Heart failure, CVA; Cerebrovascular accident, CKD; Chronic kidney disease, T; temperature, RR; respiratory rate, SBP; systolic blood pressure, DBP; diastolic blood pressure, CT; computed tomography.

Prognostic Analyses

The individual influence of any comorbidity on the outcomes is shown in Table 2. Having been regulated for sex, age, duration of hospitalization, and the presence of the other comorbidities, patients with DM (RR, 1.25 (95% CI, 1.08-1.44)), HF (RR, 1.45 (95% CI, 1.10-1.91)), CKD (RR, 1.32 (95% CI, 1.04-1.67)), malignancy (RR, 1.79 (95% CI, 1.41-2.28)), and lung diseases (RR, 1.53 (95% CI, 1.27-1.84)) were more probably to achieve the composite endpoint than those without the very comorbidity. We also estimated the effect of any comorbidity on the personal clinical outcomes through the hospital course. After adjustment for age, sex, duration of hospitalization, and the presence of the other comorbidities, patients with DM (RR, 1.31 (95% CI, 1.09-1.56)), CAD (RR, 1.37 (95% CI, 1.08-2.73)), CVA (RR, 1.52 (95% CI, 1.02-2.25)), malignancy (RR, 1.98 (95% CI, 1.44-2.71)), and lung disease (RR, 1.72 (95% CI, 1.35-2.19)) were more likely to be admitted to the ICU. Those with HTN (RR, 1.40 (95% CI, 1.06-1.85)) and malignancy (RR, 1.64 (95% CI, 1.01-2.66)) were more likely to get invasive mechanical ventilation. The patients with DM (RR, 1.50 (95% CI, 1.20-1.89)), CKD (RR, 2.03 (95% CI, 1.49-2.76)), malignancy (RR, 2.50 (95% CI, 1.74-3.61)), and lung disease (RR, 1.63 (95% CI, 1.20-2.21)) were more likely to die, compared with their counterparts without the very comorbidity.

Survival Analysis

We also inspected time-to-death during the hospital course individually for each kind of comorbidity and the number of comorbidities. The Kaplan-Meier survival curve presents the possibility of death through the hospital course in the patients with 1, 2, or 3 than 2 comorbidities (Figure 1). Cox proportional hazard regression models were implemented to detect the kind and the number of comorbidities related to death through the hospital course (Figure 2). Having been regulated for sex, age, and other comorbidities, patients with DM (HR, 1.47 (95% CI, 1.10-1.95); P = 0.008) and CKD (HR; 1.72 (95% CI, 1.16-2.56); P = 0.007) represented a meaningful increment in the hazard of death

Table 2. Comorbidities in relation with complicated hospital course in COVID-19 hospitalized patients.

Comorbidity	*Composite end-point RR(95%CI)	Death RR(95%CI)	ICU admission RR(95%CI)	Invasive ventilation RR(95%CI)
DM	1.25 (1.08-1.44)	1.50 (1.20-1.89)	1.31 (1.09-1.56)	1.04 (0.80-1.37)
HTN	1.10 (0.95-1.28)	1.21 (0.95-1.53)	1.14 (0.95-1.36)	1.40 (1.06-1.85)
CAD	1.07 (0.86-1.32)	1.00 (0.70-1.43)	1.37 (1.08-1.73)	0.71 (0.44-1.14)
HF	1.45 (1.10-1.91)	1.24 (0.83-1.87)	1.28 (0.95-1.71)	1.34 (0.78-2.31)
CVA	1.08 (0.74-1.56)	1.11 (0.65-1.87)	1.52 (1.02-2.25)	0.77 (0.38-1.54)
CKD	1.32 (1.04-1.67)	2.03 (1.49-2.76)	1.30 (0.98-1.72)	0.61 (0.33-1.12)
Malignancy	1.79 (1.41-2.28)	2.50 (1.74-3.61)	1.98 (1.44-2.71)	1.64 (1.01-2.66)
Lung disease	1.53 (1.27-1.84)	1.63 (1.20-2.21)	1.72 (1.35-2.19)	1.66 (0.85-1.88)

They are arranged for sex, age, duration of hospitalization, and other comorbidities. DM ; Diabetes mellitus, HTN; Hypertension, CAD; Coronary artery disease, HF; Heart failure, CVA; Cerebrovascular accident, CKD; Chronic kidney disease. ICU; intensive care unit.
*Composite end-point consisted any of death, ICU admission, or invasive ventilation.

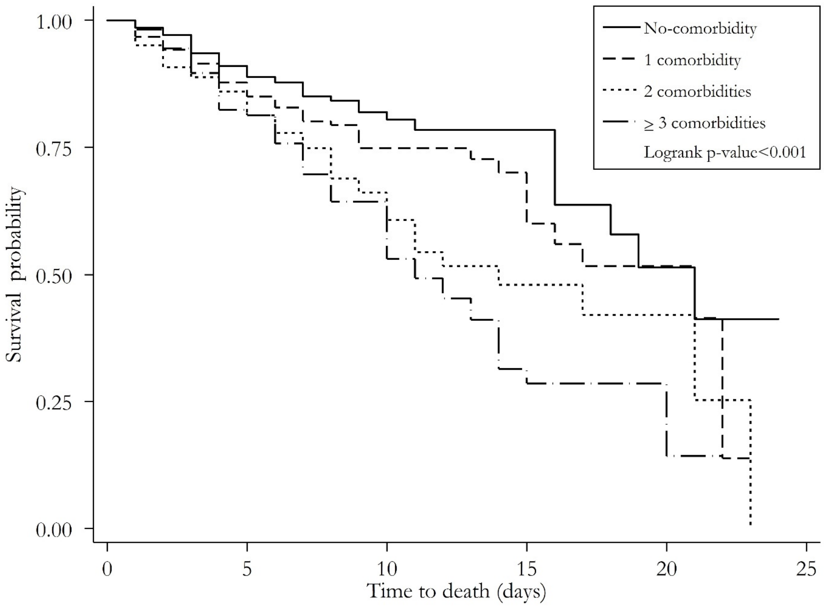

Figure 1. Kaplan-Meier survival curve categorized by the number of comorbidities

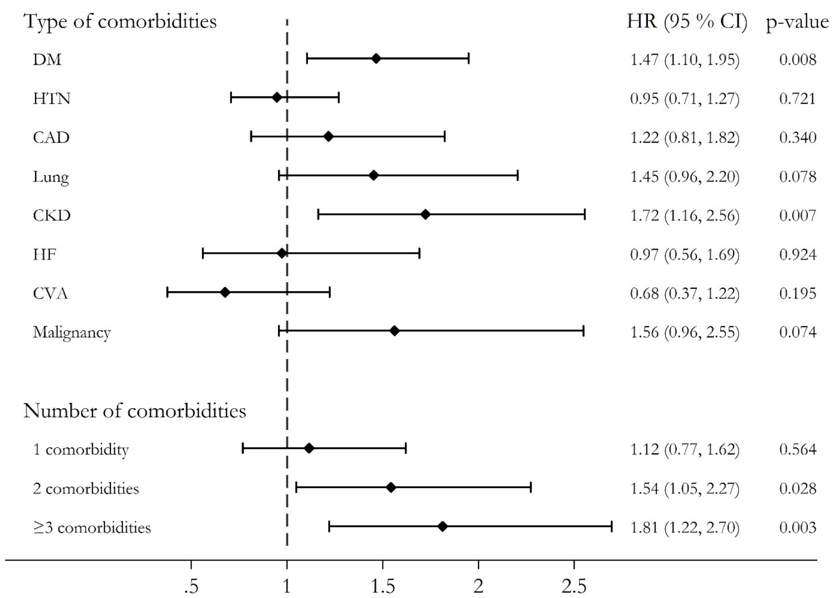

Figure 2. Predictors of death in the proportional hazard models. Hazard ratios (95% confidence interval) are shown for the comorbidities associated with the death during the hospital course. The comorbidities were classified according to the type and the number. The scale bar indicates the hazard ratio. Data were adjusted for age, sex, and other comorbidities. DM; Diabetes mellitus, HTN; Hypertension, CAD; Coronary artery disease, HF; Heart failure, CVA; Cerebrovascular accident, CKD; Chronic kidney disease.

occurrence through the hospital course compared with those without DM or CKD, respectively. In addition, compared with those patients with no comorbidity, those with 2 (HR, 1.54 (95% CI, 1.05-2.27); $P = 0.02$) and ≥3 comorbidities (HR, 1.81 (95% CI, 1.22-2.70); $P = 0.003$) were substantially at a higher risk of death through the hospital course. However, there was no meaningful variation in the risk of death between patients with 1 comorbidity and those without any comorbidity (HR, 1.12 (95% CI, 0.77-1.62); $P = 0.565$). Since age was a significant risk factor for poorer results in any comorbidities, we also fulfilled a sensitivity analysis classifying the patients by age (< 65 vs ≥ 65 years). The results described that a higher number of comorbidities are connected with a meaningful increment in the hazard of death only in patients <65 years old (2 comorbidities: OR, 2.68(1.46-4.95); $P = 0.002$) (≥3 comorbidities: OR, 3.47(1.69-7.12); $P = 0.001$). The results are presented in Figure 3.

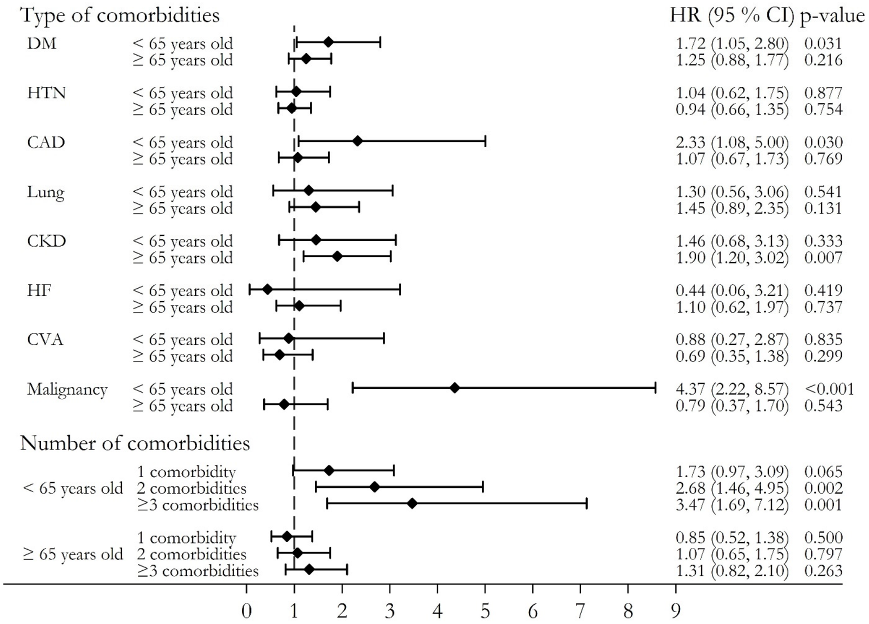

Figure 3. Predictors of death in the proportional hazard models stratified by age. Hazard ratios (95% confidence interval) are shown for the comorbidities associated with the death during the hospital course. The comorbidities were classified according to the type and the number stratified by age. The scale bar indicates the hazard ratio. Data were adjusted for age, sex, and other comorbidities. DM; Diabetes mellitus, HTN; Hypertension, CAD; Coronary artery disease, HF; Heart failure, CVA; Cerebrovascular accident, CKD; Chronic kidney disease.

Discussion

This retrospective study disclosed the kind and number of comorbidities of a complex hospital course and the intensifying risk of mortality in a broad cohort of hospitalized Iranian patients with COVID-19. Patients with CKD, HF, DM, malignancy, and lung diseases typically had greater risks of getting to the composite end-point invasive mechanical ventilation, ICU admission, or death. Moreover, those with CKD and DM had an undoubtedly expanded risk of death through the hospital course. Regarding the number of comorbidities, having ≥2 comorbidities intensified mortality risk in patients <65 years during hospitalization.

The most widespread comorbidities in this extended cohort of COVID-19 patients were HTN, DM, and CAD. These comorbidities are considered the most prevalent underlying diseases in studies with various sample sizes organized in different populations (1, 4, 15). Furthermore, meta-analyses of distinct studies, many of which had been conducted in China, described the same findings (16, 17). Based on the relatively large sample size, a spectrum of comorbidities—including HF, CVA, CKD, COPD, chronic liver disease, asthma, TB, and HIV, consistent with the results of previous studies—was investigated (1, 4, 15), although the rate of patients with these comorbidities was approximately low. This investigation could be interpreted that these cardiometabolic diseases, such as HTN, CAD, and DM, reported by the patients more likely, are extremely public across the world. Also, the detected abundance of comorbidities might illustrate the disease transmission within the particular subgroups.

Similar to the previous research (15, 18, 19), our findings represented that comorbidities—eg, lung disease (COPD and asthma), malignancy, DM, CKD, and HF—are connected to an intricate hospital course in patients with COVID-19. Although our cohort patients with known HTN did not come to the composite end-point, HTN in a large cohort of Chinese patients with COVID-19 was related to higher risk of the same composite end-point (15). This contradiction might be described by the fact that no regulation for other comorbidities was adjusted in this study. At the same time, we estimated all the other coexistence underlying diseases such as lung disease, malignancy, CKD, DM, and HF that could confound the results. Additionally, the blood pressure (BP) of the patients in our cohort was well controlled at the time of admission, with a median of 120/80 mmHg. This is important since poorly regulated BP may make it more difficult for COVID-19 patients to receive hospital care beyond being treated as hypertensive cases. Some other meta-analysis studies with approximately low sample sizes, which were not regulated for other potential risk factors, confirmed that HTN is correlated with a higher risk of ICU admission (8). Moreover, the entered studies had diverse descriptions of HTN and different requirements for ICU admission (8).

Survival analysis presented that CKD and DM considerably raised the hazard of death through the hospital course. Previous research not only showed that DM is linked to an increased risk of death (20, 21), but it also shown that different blood glucose control levels predict different outcomes in individuals with COVID-19 and prior type 2 diabetes. (22). Although some researchers established a detrimental correlation between the severity of COVID-19 and CKD (18), few verified the impact of CKD on death (25). On the contrary to the research investigated in New York

(23), we achieved a meaningful correlation between CKD and death in hospitalized patients, regarding all the possible risk factors. This contradiction might be described by the fact that the former study was a single-center study that had not include many patients. Furthermore, a suggested study demonstrated a crucial link between renal disease and in-hospital death, despite consisting of just 2% of patients with diagnosed CKD (24).

Although the coexistence of various basic diseases has been generally recorded in the cohorts of COVID-19- patients (4, 19, 25), a few demonstrated the influence of co-existing comorbidities on the clinical outcome of COVID-19 (15). Our study approved that the coexistence of ≥2 comorbidities gradually intensified the hazard of death. However, there was no distinction in the prediction of those with 1 comorbidity compared with those without any comorbidity. Regarding the intense independent role of age in the complicated hospital course and in-hospital death (23, 26), we implemented a sensitivity analysis classifying the patients based on their age (< 65 vs ≥ 65 years). We found that coexisting comorbidities have a significant detrimental impact on death in patients <65 years. According to the data presented in this study, there is no correlation between the existence of any comorbidity and the death of COVID-19 patients >65 years.

Strengths and Limitations

This was, to our knowledge, the first multicenter cohort study on Iranians with COVID-19 that looked into the connection between a variety of comorbidities and a complicated hospital stay. In addition, data on comorbidities were accessible for >90% of the admitted patients. However, this study has certain limitations. First, random sampling could not be applied in our study as a result of the necessity of data extraction. Second, comorbidities were self-reporting. Underreporting of comorbidities because of lack of awareness or diagnostic testing might distract the intensity of their corporation with the clinical results.

Conclusion

In this cohort of Iranian people with COVID-19, the presence of malignancy, DM, HF, CKD, and lung disease were prognosticator of a complicated hospital course. CKD and DM were also risk factors for in-hospital mortality. Furthermore, the risk of death was more than twice as high for patients 65 years of age or older with at least two comorbidities.

Authors' Contributions

N.T. and M.E.K. contributed to the study design. Z.E., R.A., M.H., and F.A. contributed to the data acquisition and analysis. N.H.M., M.M., and M.E.K. contributed to the data interpretation. A.K.H. cleaned and analyzed the data. N.T., N.H.M., and M.E.K. drafted or substantially contributed to revising the work. All authors read and approved the manuscript.

Ethical Considerations

N/A.

Acknowledgment

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Conflict of Interests

The authors declare that they have no competing interests.

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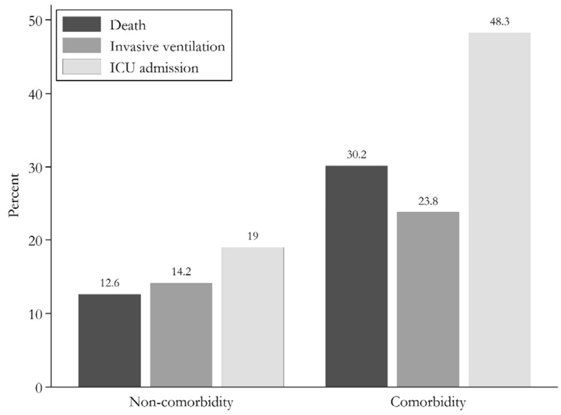

Supplementary Figure 1. Outcomes during the hospital course stratified by the presence or absence of any comorbidity. ICU; intensive care unit