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Survival Evaluation of Hospitalized COVID-19 Patients with Cox Frailty Approach

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Original Research

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Abstract

Introduction: The survival cox analysis is becoming more popular in time-to-event data analysis. When there are unobserved /unmeasured individual factors, then the results of this model may not be dependable. Hence, this study aimed to determine the factors associated with Covid-19 patients' survival time with considering frailty factor.

Methods: This study was conducted at 1 of the hospitals in Iran, so that hospitalized patients with COVID-19 were included. Epidemiological, clinical, laboratory, and outcome data on admission were extracted from electronic medical records. Gamma-frailty Cox model was used to identify the effects of the risk factors.

Results: A total of 360 patients with COVID-19 enrolled in the study. The median age was 74 years (IQR 61 – 83), 903 (57·7%) were men, and 661 (42·3%) were women; the mortality rate was 17%. The Cox frailty model showed that there is at least a latent factor in the model ($P = 0.005$). Age and platelet count were negatively associated with the length of stay, while red blood cell count was positively associated with the length of stay of patients.

Conclusion: The Cox frailty model indicates that in addition to age, the frailty factor is a useful predictor of survival in Covid-19 patients.

COVID-19 is usually asymptomatic, and its patients often improve without specialized medical care.[1] Besides, a considerable proportion of these cases intensify other diseases and acute severe respiratory failure.[2] These COVID-19 patients usually need hospitalization, intensive care unit admission, and in most cases require intubation.[3] A key feature in survival analysis is that not everyone will necessarily experience the event of interest within the specified time of the study, so some individuals are censored.[4,5]

It is possible to account for all relevant covariates in the model scarcely. These variables account for observed heterogeneity and the unaccounted part is considered unobserved heterogeneity. The effects of unobserved heterogeneity are referred to as frailty. Frailty is an unobserved individual random effect that acts multiplicatively on the hazard. The estimated variance is a preventative measure of this unobserved heterogeneity.[6,7]

Studies of the clinical and epidemiological characteristics of COVID-19 have been conducted in most countries. As 1 of the first conducted studies, Huang *et al.* revealed the clinical manifestations of these patients and observed that intensive care unit (ICU) patients had higher plasma levels of cytokines compared with non-ICU patients.[4] Jonathan Hewitt *et al.* concluded in their study that inpatients admitted to hospitals with COVID-19 disease outcomes were better predicted by frailty than either age or comorbidity. Their findings support the use of CFS to inform decision making about medical care in COVID-19 patients.[8] These studies were single-centered with univariate analysis without considering the influence of heterogeneity and unobserved or confounding factors because of their small sample sizes.[9] Hence, accounting for this factor and considering the frailty by fitting a multivariate Cox frailty model has become desirable.[10] Therefore, in this study, we used the Cox frailty hazard model to provide a highly accurate risk-estimation model to predict unmeasured factors affecting survival time among hospitalized Covid-19 patients in Birjand.

Methods

A retrospective, single-center observational study was performed among COVID-19 patients at the general hospital in Birjand, Southeast Iran. We examined a systematic random sampling from patients with COVID-19 on admission from March 1, 2020, to November 15, 2020. All hospitalized patients admitted and diagnosed with COVID-19 were included as members of the sampling list. Inclusion diagnostic criteria were positive real-time reverse transcriptase-polymerase chain reaction (RT-PCR) or a clinical diagnosis made by the radiological responsible clinician based on signs, symptoms or radiology consistent with COVID-19.

The only exclusion criteria were incomplete hospital records during data analysis that were retained from the study. Demographic variables such as age and sex were included. Selected

variables for analysis were based on prognostic indicators used including a history of coronary artery disease, diabetes, and hypertension; smoking status, and blood biomarkers in recent COVID-19 studies. Clinical, laboratory, and radiographic parameters were extracted from electronic health records. The basic outcome was time-to-death and indeed (time from hospital admission to death) in days. Patients who were still alive in the hospital at the end of follow-up, were censored for survival analysis. For patients that died, the date of death was considered for survival analysis.

Survival model with frailty component

In most cases, the assumption of community homogeneity was not established and patients with the same covariates had different survival times. This difference can be attributed to the existence of unobserved risk factors that are not included in the model. In such cases, considering the effect of these unknown factors, frailty models can be used and lead to more valid results. That is, frailty models provide more reliable results, adding common frailty to a model to account for heterogeneity between diverse groups of observations.

The specified outcome in this study was time-to-mortality and it was analyzed with the Cox frailty hazard model, containing a random effect to account for variations occurring between patients and adjusted for the above-selected variables. HRs were estimated along with 95% confidence intervals.

Statistical analysis

We first evaluated these variables individually in a univariate Cox model adjusted for age and sex. Predictors that were significant in the univariate models were further entered in multivariate models, again adjusting for age and sex. Since some crucial factors were not recorded in the data, it was a great heterogeneity between patients. Therefore, a Cox frailty model was utilized to account for unobserved variables. R version 3.6.3 (The R Foundation, Indianapolis, Indiana, USA) and the packages "survival" and "cmprsk" were used in the analysis. The significance level was set to a value of < 0.05

Ethics approval

All procedures in this study were approved by the Ethical Committee of Birjand University of Medical Sciences, reference number: IR.BUMS.REC.1399.185.

Results

Sample characteristics

From May 20, 2020, to September 20, 2020, we screened a total of 360 patients from a general hospital after the exclusion of patients with no clinical record or missing diagnosis record aged 21 years and older, who were diagnosed with COVID-19. Therefore, complete data were available for (95·4%) of included patients, imputation technique was used for missing status, and all outcomes were completed for all patients.

The hospital mortality rate in the patients with COVID-19 was 17%. This was higher among patients with COVID-19, and they were older, frailer, and had a higher prevalence of comorbidities, such as diabetes, and hypertension when compared with other patients. Most patients admitted to the hospital are middle-aged, with 75% of them being 58 years or less. A large variation was observed for clinical variables, with most ranging very abnormally.

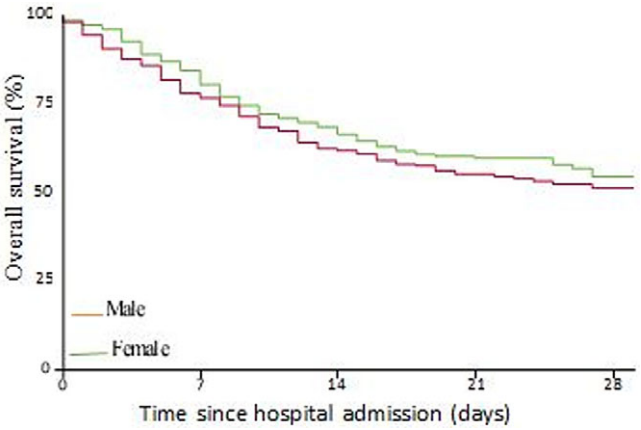

Figure 1. Overall survival by sex.

Table 3 shows that the variance of frailty is greater than 0 ($\theta = 1.82$; $P = 0.007$) significantly. It shows that there are latent factors that affect the hazard of death.

We reported the results of cox frailty model in Table 2. As findings show, age groups, gender, and comorbidity are related to the hazard rate significantly. The result of the frailty Cox model shows that the hazard of mortality due to Covid-19 in men with an age higher than 60 years is about 3.2 times compared to the men with an age less than 60 years ($P = 0.023$). Moreover, comorbidity increases the death hazard ($P = 0.002$). A negative coefficient for age categories indicated that these patients had worse prognoses, compared to those whose ages were between 18 - 39 years. However, these findings were not significant statistically. For those aged ≥ 80 years old, coronary artery disease and hypertension were also associated with mortality (HR = 2·25, 95% CI: 1·47 – 3·45; $P < 0{\cdot}001$). No difference in the radiological and clinical diagnosis of COVID-19 was observed by sex (results were not shown).

Table 1 shows the unadjusted and adjusted survival analysis between demographic, clinical variables, and frailty with time from hospital admission to discharge or death, among patients. Variables such as age and gender were associated significantly ($P < 0.001$). Hence, older ages and the male sex increased the risk of mortality. In contrast, previous admissions were not associated with mortality (HR = 0·93, 95% CI: 0·79 – 1·09).

Sex and place of residence did not differ significantly between survivors' and non-survivors' cases. However, compared to survivors of COVID-19, non-survivors were significantly older. Baseline hemoglobin, white blood cell, platelet, or 25-hydroxyvitamin D levels were not significantly different. Duration of hospitalization tended to be shorter in those who died ($P > 0.05$).

Most non-survivor patients were admitted to the ICU, so that the hazard ratio for mortality was significantly higher in patients requiring ICU admission ($P < 0.0001$).

As seen in Figure 1, females had better overall survival than males. Also, the obtained results showed that older ages had lower overalll survival (Figure 2).

Discussion

Coronaviruses are RNA positive stranded viruses that cause severe lung damage and lead to death. Epidemiological results suggest that different risk factors are related with poor prognosis in patients with COVID-19. Some known risk factors include age, obesity, high blood pressure, diabetes and heart disease.[11]

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Table 1. Characteristics of the population according to survival status

		All	Survivors (n = 313)	Non-survivors (n = 47)	Spearman (r)	*P* value
Smoking status N (%)	never	67	43	24		
	current	20	5	15	0.241	0.03
	former	13	9	4		
Sex N (%)	Male	59	32	27	0.032	0.72
	female	41	24	17		
	Urban	69	46	23	−0.262	.020
Residence N (%)	Rural	31	17	14		
Baseline hemoglobin	(Mean ± SD)	13.63 ± 2.3	12.41 ± 2.8	11.27 ± 1.9	–	0.17
White blood cell	(Mean ± SD)	13.63 ± 2.3	13.63 ± 2.3	13.63 ± 2.3	–	0.34
platelet	(Mean ± SD)	13.63 ± 2.3	13.63 ± 2.3	13.63 ± 2.3	–	
25-hydroxyvitamin D3 levels	(Mean ± SD)	19.12 ± 4.4	18.54 ± 3.7	12.17 ± 1.9	–	0.09
Duration of hospitalization	(Mean ± SD)	8.52 ± 6.3	9.2 ± 4.6	5.2 ± 3		0.031

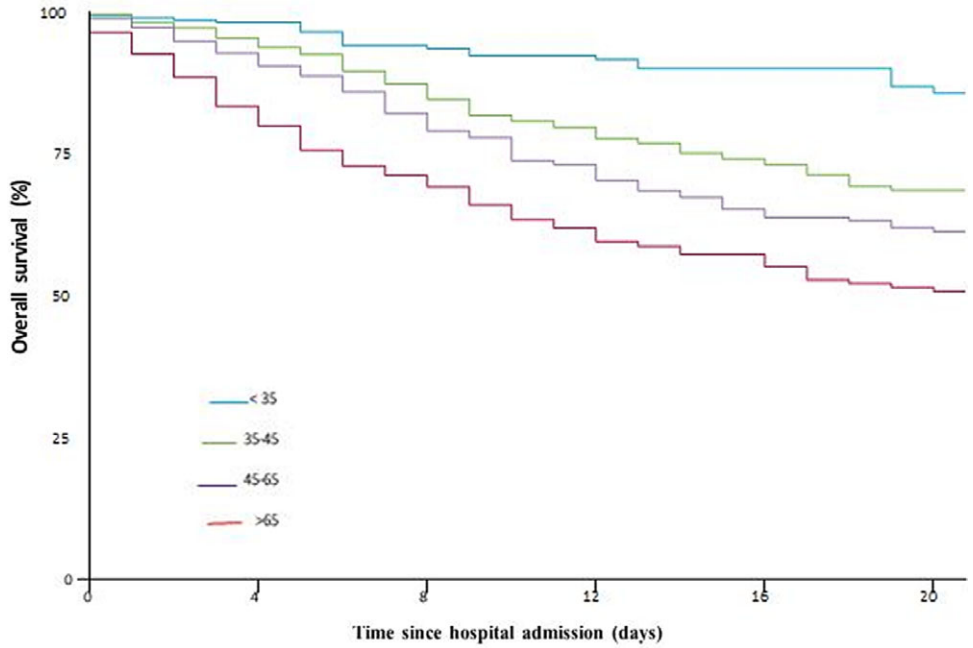

Figure 2. Overall survival by age.

Mortality in our population was 17·2%, which is in line with current mortality estimates for COVID-19 globally. A study recently showed a mortality rate of 26% in a large UK study.[12] These data also show that frailty helps to predict the hazard of death in COVID-19 patients, similar to other diseases.

Here, we fitted the frailty Cox model to estimate the adjusted hazard of Covid-19 hospitalized patients. Our results showed that a higher age group had a direct effect on the hazard of death. These results are consistent with another study.[13] The present study was performed during 3 months of follow-up. In the current study, the gamma-frailty Cox model was fitted to the COVID-19 patients. The findings represent that the increased mortality associated with increased C-reactive protein levels and prevalence of comorbidities (hypertension, diabetes, etc.) are also in line with other estimates, suggesting that our data are comparable with other populations.[14,15] It is unfortunate that because of the constraints of the pandemic, we were unable to rapidly collect more clinical data. We purposely focused only on the main variables in the study to get fast reporting of the frailty effect. Parvin Sarbakhsh *et al.* conducted a similar study in Tabriz, their findings represented that in their sample of patients with COVID-19, diabetes was an important variable related to patient survival. Also, the significant frailty effect indicates the existence of unobserved heterogeneity that causes individuals with a similar value of the observed covariates to have different survival distributions.[16]

Regarding the frailty model, the frailty component was quite significant. Although COVID-19 is very infectious and people are usually susceptible, not everyone who is exposed to the Coronavirus becomes infected. Furthermore, infected persons may have various incubations, symptoms, disease processes and outcomes.

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Table 2. Adjusted hazard rate estimation for prognostic risk factors on survival using gamma-frailty Cox model

Variables	Coefficient	SE	HR	95%CI	*P* - value
Hypertension					
Yes	0.377	0.319	1.458	0.781, 2.72	0.240
No					
Comorbidity					
Yes	0.842	0.347	2.321	1.177, 4.58	0.015
No					
Sex					
Male	0.136	0.018	1.145	1.105, 1.19	< 0.001
Female					
Smoking status					
Never					
Current	0.553	0.329	1.738	0.913, 3.31	0.093
Former	1.310	0.385	3.706	1.742, 7.89	0.001
BMI, Kg/m^2					
< 30	−0.126	0.340	0.882	0.453, 1.72	0.710
30 – 34.9	−0.086	0.352	0.917	0.460, 1.83	0.811
35 – 39.9	1.189	0.377	1.128	0.568, 3.88	0.002
> 40					
History of admissions due to Covid-19					
Yes	0.57	0.62	0·93	0.79,1.09	0.31
No					
Age group					
18 – 39 years					
40 – 49	0.219	0.377	1.021	0.268, 2.88	0.11 2
50 - 59	−0.307	0.236	0.735	0.463, 1.167	0.192
60 - 69	−0.221	0.245	0.802	0.496, 1.296	0.367
70 - 79	1.189	0.377	3.283	1.568, 6.88	0.002
≥ 80 years	2.054	0.219	2.253	1.471, 3.45	< 0.001
Frailty	1.820	–	–	–	0.005

Increasing age has been associated with COVID-19 mortality previously. Our study expresses a relationship between frailty and mortality in older patients. This finding is in line with previous studies, showing an association between frailty and non-Covid mortality as well as among older hospitalized adults.[17,18]

This study had certain limitations. First, hormonal factors have not been considered as key factors on the hazard. Second, there are missing observations in a few recorded factors. It is possible that inaccuracies may have occurred during data collection; although, our research team is experienced in collecting data. Therefore, these results are only generalizable to an inpatient population.

As a suggestion for future studies, we recommend applying rate proportional hazard model in the modeling of survival rate of Covid-19 patients.

Conclusion

As the results of the frailty model were shown, it can be concluded that accounting for latent variables including genetic factors and environmental can increase the efficacy of the predictive analysis. Also, using a more advanced statistical model that considers the role of latent variables can lead to reducing the hazard of mortality which highlights the screening role. Frailty is associated with COVID-19 mortality in older hospitalized patients. Increasing age, male sex, and comorbidities are also associated with increased death hazard. Although, we feel that it can be useful, in conjunction with other prognostic markers regarding clinical management decisions.

Data availability statement. The datasets used and/ or analyzed during the current study are available from the corresponding author on reasonable request.

Author contributions. FO and MZ designed the experiments. FO collected data, performed the statistical analyses, and wrote the results section. FO also interpreted the results and wrote the initial manuscript. MZ critically reviewed and modified the manuscript. Both authors approved the final manuscript.

Conflict of interests. The authors declare that they have no competing interests.

References

1. **Shahid Z, Kalayanamitra R, McClafferty B, *et al.*** COVID-19 and older adults: what we know. *J Am Geriatr Soc.* 2020;68(5):926-929. doi: 10.1111/jgs.16472
2. **Huang C, Wang Y, Li X, *et al.*** Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China [published correction appears in *Lancet*. Jan 30, 2020]. *Lancet.* 2020;395(10223):497-506. doi: 10.1016/S0140-6736(20)30183-5
3. **Guan WJ, Ni ZY, Hu Y, *et al.*** Clinical characteristics of Coronavirus disease 2019 in China. *N Engl J Med.* 2020;382(18):1708-1720. doi: 10.1056/NEJMoa2002032
4. **Zhou F, Yu T, Du R, *et al.*** Clinical course, and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study [published correction appears in *Lancet*. Mar 28, 2020; 395(10229):1038]. *Lancet.* 2020;395(10229):1054-1062. doi: 10.1016/S0140-6736(20)30566-3
5. **Osmani F.** Statistical ambiguities in epidemics of Coronavirus disease 2019 (COVID-19). *Acta Med Iran.* 2020;58(3):142-143.
6. **Hanlon P, Nicholl BI, Jani BD, *et al.*** Frailty and pre-frailty in middle-aged and older adults and its association with multimorbidity and mortality: a prospective analysis of 493 737 UK Biobank participants. *Lancet Public Health.* 2018;3(7):e323-e332. doi: 10.1016/S2468-2667(18)30091-4
7. **Osmani F.** Problems with the accurate reporting of COVID-19 statistics in Iran. *Gastroenterol Hepatol Bed Bench.* 2020;13(4):275-277.
8. **Hewitt J, Carter B, Vilches-Moraga A, *et al.*** The effect of frailty on survival in patients with COVID-19 (COPE): a multicenter, European, observational cohort study. *Lancet Public Health.* 2020;5(8):e444-e451. doi: 10.1016/S2468-2667(20)30146-8
9. **Zheng S, Fan J, Yu F, *et al.*** Viral load dynamics and disease severity in patients infected with SARS-CoV-2 in Zhejiang province, China, January-March 2020: retrospective cohort study. *BMJ.* 2020;369:m1443. Published Apr 21, 2020. doi: 10.1136/bmj.m1443
10. **Shears M, Takaoka A, Rochwerg B, *et al.*** Assessing frailty in the intensive care unit: a reliability and validity study. *J Crit Care.* 2018;45:197-203. doi: 10.1016/j.jcrc.2018.02.004
11. **Sun H, Ning R, Tao Y, *et al.*** Risk factors for mortality in 244 older adults with COVID-19 in Wuhan, China: a retrospective study. *J Am Geriatr Soc.* 2020;68(6):E19-E23. doi: 10.1111/jgs.16533
12. **Muscedere J, Waters B, Varambally A, *et al.*** The impact of frailty on intensive care unit outcomes: a systematic review and meta-analysis. *Intensive Care Med.* 2017;43(8):1105-1122. doi: 10.1007/s00134-017-4867-0
13. **Grasselli G, Zangrillo A, Zanella A, *et al.*** Baseline characteristics and outcomes of 1591 patients infected with SARS-CoV-2 admitted to ICUs of the Lombardy Region, Italy [published correction appears in *JAMA*. 2021;325(20):2120]. *JAMA.* 2020;323(16):1574-1581. doi: 10.1001/jama.2020.5394

14. **Smith MJ, Hayward SA, Innes SM, *et al.*** Point-of-care lung ultrasound in patients with COVID-19 - a narrative review. *Anaesthesia.* 2020;75(8): 1096-1104. doi: 10.1111/anae.15082
15. **Onder G, Rezza G, Brusaferro S.** Case-fatality rate, and characteristics of patients dying in relation to COVID-19 in Italy [published correction appears in *JAMA*. Apr 28, 2020;323(16):1619]. *JAMA*. 2020;323(18): 1775-1776. doi: 10.1001/jama.2020.4683
16. **Sarbakhsh P, Ghaffary S, Shaseb E.** Evaluation of factors related to the survival of hospitalized patients with COVID-19: survival analysis with frailty approach. Published online Aug 9, 2021. *Disaster Med Public Health Prep*. 2021;1-6. doi: 10.1017/dmp.2021.260
17. **Aw D, Woodrow L, Ogliari G, *et al.*** Association of frailty with mortality in older inpatients with Covid-19: a cohort study. *Age Ageing.* 2020; 49(6):915-922. doi: 10.1093/ageing/afaa184
18. **Kow CS, Hasan SS, Thiruchelvam K, *et al.*** Association of frailty and mortality in patients with COVID-19: a meta-analysis. *Br J Anaesth.* 2021;126(3):e108-e110. doi: 10.1016/j.bja.2020.12.002

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