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Evaluation of Factors Related to the Survival of Hospitalized Patients With COVID-19: Survival Analysis With Frailty Approach

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Abstract

Objective: Considering that coronavirus disease 2019 (COVID-19) is an emerging disease and results in very different outcomes, from complete recovery to death, it is important to determine the factors affecting the survival of patients. Given the lack of knowledge about effective factors and the existence of differences in the outcome of individuals with similar values of the observed covariates, this study aimed to investigate the factors affecting the survival of patients with COVID-19 by the parametric survival model with the frailty approach.

Methods: The data of 139 patients with COVID-19 hospitalized in Imam Reza Hospital in Tabriz were analyzed by the Gompertz survival model with gamma frailty effect. At first, variables with $P < 0.1$ in univariable analysis were included in the multivariable analysis, and then the stepwise method was used for variable selection.

Results: Diabetes mellitus was significantly related to the survival of hospitalized patients ($P = 0.021$). The rest of the investigated variables were not significant. The frailty effect was significant ($P = 0.019$).

Conclusions: In the investigated 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.

In December 2019, an increasing number of abnormal cases of pneumonia were reported in Wuhan, China. On March 11, 2020, the World Health Organization identified coronavirus disease 2019 (COVID-19) as a worldwide pandemic with a very high incidence and mortality rate. According to statistics, by March 2021, more than 120 million people have been infected with coronavirus and more than 2.6 million people have died.[1] According to reports from different countries, there are many differences in the outcome of patients; mild infection and complete recovery, hospitalization, the need for intensive care unit (ICU) stay, and death are the consequences of this disease, which are affected by different factors such as age, underlying diseases, and gender.[2–5] Identifying these factors and their impact on the patient's clinical condition can help to prevent progressing of the infection and lead to the use of appropriate treatments for patients.

It is very important to evaluate the survival time of hospitalized patients and determine the factors affecting their survival time. Ordinary survival models, such as Cox or parametric models, are methods that are suitable for analyzing survival data in homogeneous communities so that, individuals with the same value of the observed covariates have the same distribution for survival times.[6] It is possible that all covariates that can affect the survival time are not involved in the model. This means that there is unobserved heterogeneity and people with the same value of the covariates may have different survivals.[6]

Our study population, that is, patients with unknown effective characteristics on the survival times, cannot be considered homogeneous. Because seemingly similar individuals with COVID-19 have very different outcomes, from complete recovery to death, and have different survival times, it is necessary to consider this heterogeneity in some way in the analysis of survival-related factors. For this purpose, by adding a random component to the survival functions in parametric models, a factor called frailty can be added to the model, which represents unknown factors and variables. Recently, studies on the survival time of patients with COVID-19 disease have been performed by different methods,[2,5,7,8] but in none of them, the method of frailty models have been used. This study aimed to investigate the factors affecting the survival time of patients with COVID-19 admitted to Imam Reza Hospital in Tabriz from April 1 to 17, 2020, with a frailty approach.

Methods

This study is a secondary study and contains information about some patients with COVID-19 whose data had been collected during the approved study with the code of ethics IR.TBZMED.REC.1398.1310.

In that randomized clinical trial, several patients who had laboratory or clinical-confirmed COVID-19 infection had been included. Patients had been recruited from Imam Reza Hospital in Tabriz, Iran between March 20 and April 5, 2020. Pregnant women, patients with type I diabetes, ketoacidosis, heart failure, severe kidney failure (glomerular filtration rate [GFR] < 30 mL/min), severe respiratory failure, retinopathy, G6PD deficiency, and children had been excluded from the study. The present study is observational, and 139 patients who had participated in the original study and underwent the normal course of treatment in Imam Reza Hospital were included in this study (E. Shaseb et al. unpublished data, 2021).

Statistical Analysis

In the present study, continuous variables were described as means (standard deviation [SD]) for symmetric variables and median (interquartile range [IQR]) for asymmetric variables. Categorical variables were expressed as number and percentage (%). The death consequence was considered as the event and the survival of patients was time to death, constructed as the time between the date of admission and death with censoring on discharge date for individuals who were alive by the time of discharge. The Kaplan-Meier method was used to estimate the median survival time.

Survival time that is considered from the moment of hospitalization to death or discharge as the dependent variable and demographic information, comorbidities, vital signs of the patient at the time of hospitalization, variables related to the severity of the disease (computed tomography [CT] scan of the lungs and the lung involvement amount) were considered as the independent variable, and their effect on the survival time of hospitalized patients with COVID-19 was evaluated.

The demographic and clinical factors affecting the survival of hospitalized patients were investigated by the parametric survival model with gamma frailty effect. In this study, the Akaike information criterion (AIC) was used to model selection (among Weibull, Gompertz, log-logistic, exponential, and lognormal distributions for survival time). The smaller value for this criterion means a better and more suitable model.

To identify the effective variables, due to a large number of variables, for variable selection, first, we fit univariable parametric survival models with the gamma frailty effect, to examine the effect of all demographic and clinical variables on patients survival time. Then by using the univariable selection algorithm for variable selection,[9] the variables with $P < 0.1$ in the univariable models were selected to include in the multivariable parametric survival model with the gamma frailty effect. The backward stepwise selection method (removing terms with $P \geq 0.2$ and adding those with $P < 0.1$) was used for final variable selection in the multivariable model.

For evaluation of the proportionality assumption for parametric proportional hazard (PH) models, survival probability was estimated for the final model and log (-log (survival) values were plotted against survival time.

The significance level of tests was set at 0.05 and 2-tailed tests were performed. All analyzes were performed using STATA14 software.

Parametric Survival Models With Parametric Frailty Component

The response variable in survival models is the time until an event occurs. This time can be censored. The semi-parametric Cox proportional hazards model is one of the most common models for analyzing survival data. One of the assumptions of this method is the homogeneity of people in the population. The parametric approach is another method of survival analysis that can be considered different distributions, such as Weibull, log-normal, gamma, etc., for survival time.[10] These models are also based on the assumptions of community homogeneity, independence, and identical distribution of survival data. But in many cases, the risks of statistical units are different and the assumption of community homogeneity is not established and patients with the same covariates have different survival times. One of the reasons for this difference can be attributed to the existence of unknown or unobserved risk factors that are not included in the model, and disregarding them can lead to invalid results. In such cases, to consider the effect of these unknown factors, semi-parametric or parametric frailty models can be used, which consider the effect of these unknown factors in the form of a random component and lead to more valid results.

These types of models have been proposed as a method for considering the dependency between observations,[6] which, in addition to including independent variables in the model, also include unobserved effects that affect survival time in the model. Failure to consider these common unknown risk factors creates a correlation between survival times. In such a case, the use of parametric and Cox survival models is inappropriate and the frailty model provides more reliable results. Adding common frailty to a model has the same role as adding a random effect to the classical linear regression model, as a way to account for heterogeneity between different groups of observations. In general, the frailty model has a random component that is defined as a conditional hazard model:

$$h_{ij}(t|u_i) = h_0(t)\, u_i\, \exp(X'_{ij}\beta) = u_i h_{ij}(t);\; i = 1, \ldots, G, j = 1, \ldots n_i$$

Where $h_0(t)$ is the base hazard function, u_i is the frailty factor of i$^{\text{th}}$ group, x_{ij} the vector of explanatory variables for j$^{\text{th}}$ subject in i$^{\text{th}}$ group, and β the vector of regression coefficients. Also, the survival function of j$^{\text{th}}$ subject in i$^{\text{th}}$ group in t$^{\text{th}}$ time will be as follows, considering the relationship between the survival function and hazard:

$$S_{ij}(t|X_{ij}, u_i) = \exp\{-H_0(t) u_i \exp(X'_{ij}\beta)\}$$

That $H_0(t) = \int_0^t h_0(v)dv$ is the cumulative baseline hazard function. In this approach, the baseline hazard function and the distribution of the frailty random factor (with specific mean and variance) are considered as parametric functional forms in the hazard model.[6]

Results

Of the 139 patients admitted to the hospital, 65 were female (46.8%) and 74 were male (53.2%). Fifteen patients (10.8%) died before discharge. Using the Kaplan-Meier method, the median survival time of these patients was estimated to be 20.00 d (95% confidence interval [CI]: 13.66-26.33) from the time of admission, which was 51 d for women and 15 d for men.

Table 1. Demographic and clinical characteristics of the patients

Characteristics		Dead ($n = 15$)	Alive ($n = 124$)	P-Value*
Demographic	Age (y)	68.73 ± 11.60	59.59 ± 15.88	0.323
	Gender (male)	8 (53.3%)	66 (53.2%)	0.468
	BMI kg/m^2	28.88 ± 4.91	28.81 ± 4.99	0.952
	Smoking (yes)	1 (6.7%)	3 (3.0%)	0.656
Vital sign	SPO_2 %	85.51 ± 4.84	89.80 ± 4.60	0.223
	Respiratory rate (breaths per min)	22.00 ± 3.50	23.01 ± 9.49	0.715
	Pulse rate (beats per min)	87.40 ± 12.53	87.31 ± 14.40	0.782
	SBP (mmHg)	130.00 ± 9.06	122.08 ± 15.38	0.314
	DBP (mmHg)	84.33 ± 6.77	77.18 ± 9.45	0.221
	Temperature	37.52 ± .61	37.25 ± 0.68	0.339
Laboratory findings	WBC	5550.4 (3900)	6900 (4600)	0.320
	Neutrophil	87.00 (17.50)	79.00 (15.00)	0.123
	Lymphocyte	11.10 (15.00)	19.65 (13.68)	0.077
	Hemoglobine	12.20 (2.50)	13.20 (2.63)	0.876
	Platelet	172.0 (64.00)	177.00 (115.00)	0.768
	Creatinine (mg/dL)	1.20 (.62)	1.00(.31)	0.778
	AST(units/L)	33.00 (18.00)	29.00 (22.00)	0.001
	ALT(units/L)	25.00 (18.00)	23.00 (16.75)	<.001
	LDH(units/L)	662.00 (290.00)	507.00 (201.00)	0.020
	CPK(units/L)	268.00 (210.00)	107.00 (103.00)	0.459
	Sodium (mEq/L)	135 (4)	136.00 (4)	0.092
	Potassium (mEq/L)	4.30 (.90)	4.00 (.60)	0.881
	Magnesium(mg/dL)	2.00 (.40)	2.00 (.40)	0.802
	PT(s)	14.25 (2.30)	13.70 (1.75)	0.930
	PTT(s)	35.50 (8.00)	33.00 (7.00)	0.092
	INR (ratio)	1.05 (.09)	1.02 (.08)	0.686
Symptoms	Fever (yes)	8 (53.3%)	59 (47.6%)	0.622
	Cough (yes)	11 (73.3%)	96 (77.4%)	0.446
	Dyspnea (yes)	11 (73.3%)	85 (68.5%)	0.861
	Myalgia (yes)	5 (33.3%)	68 (54.8%)	0.308
	Diarrhea (yes)	1 (6.7%)	14 (11.3%)	0.744
	Abdominal pain (yes)	0 (0.0%)	7 (5.6%)	0.998
	Headache (yes)	2 (13.3%)	17 (13.7%)	0.915
	Nausea (yes)	2 (13.3%)	19 (15.3%)	0.384
	Loss of appetite (yes)	1 (6.7%)	14 (11.3%)	0.461
	Weakness (yes)	4 (26.7%)	29 (23.4%)	0.281
	Shivering (yes)	2 (13.3%)	23 (18.5%)	0.323
		Dead ($n = 6$)	Alive ($n = 100$)	
Sensory complication	Taste (yes)	0 (0.0%)	44 (44.0%)	–**
	Smell (yes)	0 (0.0%)	50 (50.0%)	–
	Hearing (yes)	0 (0.0%)	10 (10.2%)	–

Note: Continuous variables were described as means ± SD for symmetric variables and median (IQR) for asymmetric variables. Categorical variables expressed as number (percentage [%]). Abbreviations: BMI, body mass index; PCR, polymerase chain reaction; SPO2, oxygen saturation; SBP, systolic blood pressure; DBP, diastolic blood pressure; WBC, white blood cell; CPK: creatine phosphokinase; PT: prothrombin time.
*From univariable Gompertz survival model with gamma frailty.
**Not converged.

According to the AIC criterion, among different univariable models for survival analysis, for most variables the Gompertz parametric model with the gamma frailty effect had smaller value than other distributions; so, this model was selected for univariable modeling.

By fitting a univariable Gompertz parametric model with the gamma frailty effect, the effect of all demographic variables, comorbidities, and clinical characteristics of the patients on survival time was investigated. The results have been reported in Table 1–3. According to the results, the laboratory indices of lymphocyte, aspartate aminotransaminase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), sodium, and partial thromboplastin time (PTT) as well as having diabetes, CHF, and having chronic kidney disease (CKD) with $P < 0.1$ were considered as potentially important variables to include in multivariable modeling.

Table 2. Comorbidities information

Characteristics		Dead ($n = 15$)	Alive ($n = 124$)	P value*
Comorbidities	Diabetes (yes)	10 (66.7%)	33 (26.7%)	0.019
	Hypertension (yes)	10 (66.7%)	49 (39.5%)	0.142
	Hyperlipidemia (yes)	6 (40.0%)	16 (12.9%)	0.187
	IHD (yes)	6 (40.0%)	18 (14.5%)	0.266
	CHF (yes)	1 (6.7%)	2 (1.6%)	0.079
	Hypothyroidism (yes)	0 (0%)	7 (5.6%)	0.999
	CKD (yes)	1 (6.7)	1 (.8%)	0.040
	Asthma(yes)	1 (6.7%)	9 (7.3%)	0.831
	COPD (yes)	0 (0.0%)	6 (4.8%)	0.999

Note: Categorical variables expressed as number (percentage [%]).
Abbreviations: IHD, ischemic heart disease; CHF, chronic heart failure; COPD, chronic obstructive pulmonary disease.
*From univariable Gompertz survival model with gamma frailty.

Table 3. Lung-related imaging findings and involvement scores

Characteristics		Dead ($n = 4$)	Alive ($n = 60$)	P-Value*
Involvement	CT peri/bilateral	4 (100%)	55 (97.1%)	-**
	CT peri/unilateral	0 (0%)	4 (6.7%)	
	CT Central/unilateral	0 (0.0%)	1 (1.07%)	
Total lung involvement (%)	<5	2 (50.0%)	22 (36.7%)	0.192
	5-25%	0 (0%)	22 (36.7%)	
	26-49%	1 (25.0%)	8 (13.3%)	
	50-75%	1 (25.0%)	4 (6.7%)	
	>75%	0 (0.0%)	4 (6.7%)	

Note: Categorical variables expressed as number (percentage %).
*From univariable Gompertz survival model with gamma frailty.
** Not converged.

Table 4. Results of stepwise multivariable Gompertz survival model with gamma frailty

Variable	Hazard ratio	95% CI for hazard ratio	P-Value*
Having diabetes	13.48	(1.48, 122.73)	0.021
Having CKD	23.35	(0.46, 1162.74)	0.114
Frailty component	5.21	(1.29, 20.98)	0.019

*From multivariable Gompertz survival model with gamma frailty.

Among multivariable models (including lymphocyte, AST, ALT, LDH, sodium, PTT, having diabetes, CHF, and CKD), the Gompertz parametric model (among Weibull, log-logistic, exponential, and lognormal distributions) with the gamma frailty effect had the lowest AIC value (AIC = 92.55); so, this model was selected for multivariable modeling.

The results of the backward stepwise Gompertz multivariable analysis (Table 4) confirmed that among the mentioned variables, the variable of diabetes mellitus with $P = 0.021$ had a significant relationship with the survival time of patients hospitalized with COVID-19, and despite the wide confidence interval, having diabetes significantly decreases the survival of the patients (hazard ratio = 13.48; 95% CI: 1.48-122.73).

Although the final model just included diabetes mellitus as the significant variable, the variable of CKD with $P = 0.114$ also showed a potential effect on survival time. The rest of the studied variables in this sample of patients with $P > 0.2$ did not show a significant relationship with the patient's survival time.

Furthermore, in the final model, the frailty component was significant ($P = 0.019$), which means that, first, the effect of unknown factors in the form of individual differences on patient survival is quite significant and individuals with the same explanatory variables and similar recorded characteristics had different survival times and, second, considering the contribution of these unknown factors in the analysis of the desired factors on survival improves the efficiency of the model and more reliable results and increases the model power.

Regarding the proportionality assumption for the final model, about diabetes, the graph of the log (-log [survival]) versus survival time resulted in parallel lines for 2 levels of this variable. For CKD, due to the low number of patients with CKD, the proportionality assumption was not evaluated. So, according to the results, we can conclude that the proportionality assumption was established for the final model.

Discussion

Coronavirus is a new virus first reported in China in December 2019 and has led to a global epidemic. Coronaviruses are RNA-positive stranded that cause severe lung damage and lead to death.[11] Epidemiological findings suggest that several risk factors are associated with poor prognosis in patients with COVID-19. Some known risk factors include age, obesity, high blood pressure, diabetes, CKD, and heart disease.[4]

Numerous studies have been performed in Iran[5,12] and the world[2,7] on the survival of patients with coronary heart disease. However, in these studies, the frailty approach is not considered to have more reliable estimates. In this study, the effect of variables on survival was investigated by a parametric model of survival with a frailty approach and taking into account the effect of unknown factors in the model.

According to the results, in the univariable analysis, several prognostic factors for death in COVID-19 patients admitted to Imam Reza Hospital in Tabriz were identified, but the results of the multivariable analysis showed that, in the present sample, having diabetes and CKD were important predictors of survival time of patients with COVID-19.

Regarding diabetes, many studies have shown the effect of this comorbid disease on reducing the survival of patients with COVID-19, including a meta-analysis to identify the predictors of mortality in hospitalized patients with COVID-19 conducted in 2020 and according to the results diabetes, as the second most common comorbid disease in patients, is associated with a 2-fold increased odds of COVID-19 mortality.[4] Also, a study on the survival of patients with COVID-19 reported the adjusted relative risk of death for diabetic hospitalized patients equals 1.23, which was significant.[13]

Regarding CKD, studies consistent with our findings[2,8,14,15] show that chronic kidney disease is associated with an increased risk of mortality and decreased survival of hospitalized patients. Although in general, the risk of death in people with CKD due to various infections is higher, the mechanism of its effect on mortality in patients with COVID-19 is not clear and needs further investigation.

Regarding the variables of the severity of lung involvement, although they can be important variables in predicting the patient's survival time, in the present sample, due to the small sample size, reliable results were not obtained by scanning the lungs. We propose a more detailed evaluation of the association between the severity of lung involvement and the survival of patients.

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.[16] Furthermore, infected persons may have various incubations, various symptoms, various disease processes, and various outcomes.[17,18] For example, in people of 1 family who were exposed to new coronavirus (severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]) simultaneously, the disease displayed various symptoms and outcomes among the family members.[19] This unobserved heterogeneity was accounted for in the frailty model as the random effect (frailties). The significant frailty component indicates the existence of unknown and unidentified variables involved in the survival times of the patients with COVID-19. This means that there is unobserved heterogeneity and patients with COVID-19 with a similar value of the observed covariates have different survivals, which can be attributed to genetic issues, nutrition, lifestyle, and so on.

Conclusions

In the investigated sample of patients with COVID-19, diabetes and CKD were important variables related to patient survival. There was also a significant frailty effect and indicates the presence of unknown variables that cause differences in patient survival with similar known and observed characteristics, so we need further studies to identify unknown factors associated with mortality of COVID-19.

Limitations

One of the major limitations of this study was the small number of investigated patients due to the difficulty and strict restrictions for collecting data from patients with COVID-19 and as a result, the small number of death events to study factors affecting the survival time of patients that lead to the wide confidence intervals for estimations and the nonconvergence of the model. It is recommended that other observational studies with larger sample sizes be performed on hospitalized patients to identify factors affecting the survival of these patients. The strengths of this study were the good quality of the data, a large number of variables examined, and the accurate recording of information by the research team itself.

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References

1. **WorldOmeter**. COVID-19 coronavirus pandemic 2021. https://www.worldometers.info/coronavirus/. Accessed August 26, 2021.
2. **Salinas-Escudero G, Carrillo-Vega MF, Granados-García V, *et al.*** A survival analysis of COVID-19 in the Mexican population. *BMC Public Health.* 2020;20(1):1616.
3. **Shang Y, Liu T, Wei Y, *et al.*** Scoring systems for predicting mortality for severe patients with COVID-19. *EClinicalMedicine.* 2020;24:100426.
4. **Tian W, Jiang W, Yao J, *et al.*** Predictors of mortality in hospitalized COVID-19 patients: a systematic review and meta-analysis. *J Med Virol.* 2020;92(10):1875-1883.
5. **Zandkarimi E, Moradi G, Mohsenpour B.** The prognostic factors affecting the survival of Kurdistan Province COVID-19 patients: a cross-sectional study from February to May 2020. *Int J Health Policy Manag.* 2020. doi: 10.34172/ijhpm.2020.155
6. **Balan TA, Putter H.** A tutorial on frailty models. *Stat Methods Med Res.* 2020;29(11):3424-3454.
7. **Atlam M, Torkey H, El-Fishawy N, *et al.*** Coronavirus disease 2019 (COVID-19): survival analysis using deep learning and Cox regression model. *Pattern Anal Appl.* 2021. doi: 10.1007/s10044-021-00958-0
8. **Di Castelnuovo A, Bonaccio M, Costanzo S, *et al.*** Common cardiovascular risk factors and in-hospital mortality in 3,894 patients with COVID-19: survival analysis and machine learning-based findings from the multicentre Italian CORIST Study. *Nutr Metab Cardiovasc Dis.* 2020;30(11):1899-1913.
9. **Heinze G, Wallisch C, Dunkler D.** Variable selection – a review and recommendations for the practicing statistician. *Biom J.* 2018;60(3):431-449.
10. **Kleinbaum DG, Klein M.** *Survival Analysis, A Self-Learning Text.* 3rd ed. New York: Springer; 2012.
11. **Zumla A, Hui DS, Azhar EI, *et al.*** Reducing mortality from 2019-nCoV: host-directed therapies should be an option. *Lancet.* 2020;395(10224):e35-e36.
12. **Eshrati B, Baradaran HR, Erfanpoor S, *et al.*** Investigating the factors affecting the survival rate in patients with COVID-19: a retrospective cohort study. *Med J Islam Repub Iran.* 2020;34(1):618-626.
13. **Dennis JM, Mateen BA, Sonabend R, *et al.*** Type 2 diabetes and COVID-19-related mortality in the critical care setting: a national cohort study in England, March-July 2020. *Diabetes Care.* 2021;44(1):50-57.
14. **ERA-EDTA Council; ERACODA Working Group**. Chronic kidney disease is a key risk factor for severe COVID-19: a call to action by the ERA-EDTA. *Nephrol Dial Transplant.* 2020;36(1):87-94.

15. **Pakhchanian H, Raiker R, Mukherjee A, *et al.*** Outcomes of COVID-19 in CKD patients. a multicenter electronic medical record cohort study. *Clin J Am Soc Nephrol.* 2021:16(5):785-786.
16. **Shi Y, Wang Y, Shao C, *et al.*** COVID-19 infection: the perspectives on immune responses. *Cell Death Differ.* 2020;27(5):1451-1454.
17. **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.
18. **Chan JF-W, Yuan S, Kok K-H, *et al.*** A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. *Lancet.* 2020;395(10223): 514-523.
19. **Sun J, Jiang Y, Lin W, *et al.*** Different outcome of COVID-19 in members of a family. *J Infect Dev Ctries.* 2020;14(5):447-449.