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The Effect of Age-Threshold on COVID-19 Patients Cure Rate: A Historical Cohort Study

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Abstract

Background: The COVID-19 pandemic had caused unexpected strain on healthcare systems in most countries in 2020. Although different survival models were used in clinical decision-making for COVID-19 patients, the effect of different risk factors in patients has not been identified clearly. Elderly patients, especially with comorbidities, were introduced as the most susceptible group at the risk of death. This study aimed to determine the threshold of age that influences chronic diseases and other factors that increase the cure rate of COVID-19 patients.

Methods: This observational study was conducted at Shahid Sadoughi hospital in Yazd, Iran. All participants were older than 18 years old with confirmed COVID-19 and completed the day-30 and day-180 follow-ups. The Bayesian method was used through the cure rate models, practical models in survival with a single change-point to detect the threshold of age, illustrating each risk factor's effect on the cure rate of patients.

Results: The analysis included 901 confirmed COVID-19 cases with a mean age of 54.93 ± 17.37 years. From all, 58.7% (n = 529) were men and 9.9% (n = 83) death occurrences were recorded. Sixty-five years of age was estimated as the effective change-point that could change the cure rate of patients at the end of the follow-up times.

Conclusion: The cure rate at any time during 30 and 180 follow-up days was noticeably higher in COVID-19 patients younger than 65 years who had cancer.

Keywords: COVID-19, Mortality, Age, Survival, Bayesian method

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Introduction

The pandemic caused by the new coronavirus, SARS-CoV-2 called COVID-19, became one of the most critical health challenges worldwide in 2020. By the 20th May 2020, more than 126 949 cases and almost 7183 deaths by COCID-19 were reported in Iran, although the incidence and mortality rate was rising. Iran was the first country in the number of cases (2346) in the Eastern Mediterranean and had the highest mortality rate (1).

Yazd located in the center of Iran, accounted for 6020 of all cases reported in the country. Yazd is one of the most popular medical tourism destinations for southern provinces might unintentionally enhance transmission. As a result, although the most prominent and well-equipped hospital was allocated for admission of COVID-19 patients, the intensive care units (ICUs) were mostly full, and the mortality rate of hospitalized patients was rising.

Older age, male gender, and the presence of comorbidities were reported as the factors that could increase the risk of severe disease or death (2,3). Evaluation of the instantaneous rate of death during follow-up, especially in patients with systemic diseases, is critical to determine the priorities and proper strategies for controlling the COVID-19 epidemic. Most of the studies categorized continues variables to evaluate the impact of them in death rate and neglected the effectiveness of the thresholds in cured fraction of patients. Therefore, this study aimed to scrutinize the identified risk factors' effects on the cure rate of confirmed COVID-19 patients and to detect the accessible change-point of effective continuous variables using Bayesian method in survival analysis.

Material and Methods

Study design

This manuscript was written according to the STROBE statement for writing a report of historical cohort research. This research is a single-center observational

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study conducted at Shahid Sadoughi hospital of Yazd in Iran.

Participants

All patients aged 18 years or older admitted to Shahid Sadoughi Hospital of Yazd between 20th February and 20th May 2020 and diagnosed with laboratory-confirmed SARS-CoV-2-positive swabs, clinically confirmed by the clinicians based on defined symptoms or radiology-confirmed COVID-19 cases were included. All information was recorded according to report format using routinely in Shahid Sadoughi hospital and patients with incomplete and contradict records of demographic variables or follow-up time were excluded.

Data collection

Data were recorded from one of the University Hospitals of Yazd (Shahid Sadoughi hospital) allocated for admission of COVID-19 patients. This site received both self-referred patients and unwell people triaged by paramedic staff or clinicians. The referred patients were overseen by COVID-19 specialists, including emergency physicians. All information was gathered according to the case report format being used routinely for recording.

Study outcomes

The primary outcome was mortality in diagnosed COVID-19 patients admitted to the hospital and completed the 30-day follow-up time until 20th June 2020. The date of admission was used as the date of diagnosis, and patients who were live at the latest time of the follow-up were considered censored. The second prespecified outcome was long-term mortality (180-day follow-up time), defined as the time of diagnosis until death/end of follow-up time (20th November 2020).

Statistical analysis

The paper describes demographic and epidemiological variables using means and standard deviations (±SD), frequency, and percentage (%). The χ^2 test was performed for comparing the difference between variables in survived and expired groups. The Kaplan-Meier method and log-rank test were used to plot and estimate survival distributions by each independent variable. A Cox's proportional hazards model was fitted, including significant variables in preliminary analysis using a stepwise process. In addition, the potential threshold of the effective quantitative covariates on survival was determined using the Bayesian approach by considering the cure proportion of patients using R software (https://cran.r-project.org/) (4). P value < 0.05 was considered statistically significant.

Results

Nine hundred and one confirmed COVID-19 cases were analyzed. They presented a median of 55 years (IQR: 40-68) and a mean of 54.93 ± 7.37 years of age. A higher frequency of men, 58.70% (n = 529), was observed, and the percentages of patients who died at the end of 30-day and 180-day follow-ups were 9.9% (n = 89) and 11.3% (n = 102), respectively. Patients less than or equal to 65 years of age accounted for about 70% of the recorded data and the majority (69.9%) of patients older than 65 years died at the end of 180-day follow-up (P < 0.001). Regarding the comorbidities, despite the chronic kidney disease, a higher frequency of cardiovascular disease, diabetes, hypertension, and asthma was observed in the expired group (P < 0.05). The disease caused death in both sexes and smoking groups almost in the same proportion. While patients with fatigue represented a significant difference in death percentages in both following times, common symptoms were observed in most patients without increasing the frequency of death noticeably. With regard to outcome variables, about 8% (n = 71) of the patients admitted in ICU and death occurred in 64% (n = 57) of them (P < 0.001). A median of 60 days and 215 days since the diagnosis until death/end of 30-day and 180-day follow-up time were identified, respectively (Table 1).

With regard to survival analysis, 89 deaths and 102 deaths by COVID-19 were analyzed in 901 people at risk at the end of 30-day and 180-day follow-up, respectively. Evaluating Kaplan-Meier survival function at the end of 30-day follow-up time represented 99% of survival probability in the 1st day, 93% in the 10th, and 90% in the 30th day of follow-up. Kaplan-Meier survival function at the end of 180-day follow-up time estimated 94% of survival probability in the 40th day and 89% in the 180th day.

According to log-rank test, differences in the survival probabilities at the end of 30-day follow-up were observed based on the age groups (P < 0.001), clinical history (P < 0.001), cardiovascular disease (P = 0.047), diabetes (P = 0.002), hypertension (P < 0.001), asthma (P = 0.02), cancer (P < 0.001), and ICU admission (P < 0.001) (Figure 1A). Furthermore, the log-rank test results presented significant differences in survival functions at the end of 180-day follow-up based on the age groups (P < 0.001), clinical history (P < 0.001), cardiovascular disease (P = 0.01), diabetes (P = 0.001), hypertension (P < 0.001), asthma (P = 0.047), cancer (P < 0.001) and ICU admission (P < 0.001) (Figure 1B).

Cox regression model was fitted on variables associated with death in survival curves, except ICU admission due to bias reduction. After adjustment, 3.84 higher risk in patients older than 65 years (95% CI 2.24-6.47; P < 0.001) at the end of 30-day follow-up and 4.03 higher risk in patients older than 65 years (95% CI 2.41-6.74; P < 0.001) at the end of 180-day follow-up was identified. Besides, after adjustment at the end of 30-day and 180-day follow-

Table 1. Clinical and demographic characteristics and hazard ratios of death in patients aged ≥ 18 years with confirmed COVID-19

Variable		All population 901 (100%)	At the end of 30-day follow-up			At the end of 180-day follow-up		
			Survived 812 (90.1%)	Died 89 (9.9%)	*P* value	Survived 99 (88.7%)	Died 102 (11.3%)	*P* value
Age (y)	< 65 (ref)	626 (69.5%)	598 (73.6%)	28 (31.5%)	< 0.001	595 (74.5%)	31 (30.4%)	< 0.001
	≥ 65	275 (30.5%)	214 (26.4%)	61 (68.5%)		204 (25.5%)	71 (69.6%)	
	HR (95% CI)		3.84 (2.24- 6.47)			4.03 (2.41- 6.74)		
Gender	Female	372 (41.3%)	335 (41.3%)	37 (41.6%)	0.95	331 (41.4%)	41 (40.2%)	0.812
	Male	529 (58.7%)	477 (58.7%)	52 (58.4%)		468 (58.6%)	61 (59.8%)	
Smoking	Never smokers	723 (93.7%)	657 (93.6%)	66 (94.3%)	0.82	648 (93.8%)	75 (92.6%)	0.68
	Current smokers	49 (6.3%)	45 (6.4%)	4 (5.7%)		43 (6.2%)	6 (7.4%)	
Clinical history	No	247 (30.7%)	240 (33.2%)	7 (8.5%)	< 0.001	240 (33.8%)	7 (7.5%)	< 0.001
	Yes	557 (69.3%)	482 (66.8%)	75 (91.5%)		471 (66.2%)	86 (92.5%)	
	HR (95% CI)		2.00 (0.82- 4.09)			2.19 (0.90- 5.29)		
Cardiovascular disease	No	744 (91.9%)	673 (92.6%)	71 (85.5%)	0.027	666 (92.9%)	78 (83.9%)	0.003
	Yes	66 (8.1%)	54 (7.4%)	12 (14.5%)		51 (7.1%)	15 (16.1%)	
	HR (95% CI)		1.10 (0.57- 2.12)			1.19 (0.65- 2.18)		
Type 2 diabetes	No	580 (71.6%)	533 (73.3%)	47 (56.6%)	0.001	527 (73.5%)	53 (57%)	0.001
	Yes	230 (28.4%)	194 (26.7%)	36 (43.4%)		190 (26.5%)	40 (43%)	
	HR (95% CI)		1.32 (0.81- 2.15)			1.27 (0.8- 2.02)		
Hypertension	No	534 (65.9%)	469 (68.3%)	38 (45.2%)	< 0.001	493 (68.9%)	41 (43.6%)	< 0.001
	Yes	276 (34.1%)	230 (31.7%)	46 (54.8%)		223 (31.1%)	53 (56.4%)	
	HR (95% CI)		1.13 (0.67- 1.91)			1.17 (0.7- 1.93)		
Asthma	No	714 (88.1%)	648 (89.1%)	66 (79.5%)	0.01	639 (89.1%)	75 (80.6%)	0.02
	Yes	96 (11.9%)	79 (10.9%)	17 (20.5%)		78 (10.9%)	18 (19.4%)	
	HR (95% CI)		1.36 (0.74- 2.5)			1.32 (0.73- 2.37)		
Chronic kidney disease	No	762 (94.1%)	686 (94.4%)	76 (91.6%)	0.3	677 (94.4%)	85 (91.4%)	0.24
	Yes	48 (5.9%)	41 (5.6%)	7 (8.4%)		40 (5.6%)	8 (8.6%)	
Cancer	No	790 (97.7%)	717 (98.8%)	73 (88%)	< 0.001	707 (98.7%)	83 (89.2%)	< 0.001
	Yes	19 (2.3%)	9 (1.2%)	10 (12%)		9 (1.3%)	10 (10.8%)	
	HR (95% CI)		3.88 (1.75- 8.60)			3.53 (1.60- 7.78)		
Symptoms	Fever	500 (56.2%)	453 (56.4%)	47 (54%)	0.67	450 (57%)	50 (50%)	0.18
	Cough	569 (63.9%)	514 (64%)	55 (63.2%)	0.88	509 (64.4%)	60 (60%)	0.38
	Fatigue	510 (57.3%)	447 (55.7%)	63 (72.4%)	0.003	441 (55.8%)	69 (69%)	0.01
	Other	621 (69.8%)	566 (70.5%)	55 (63.2%)	0.16	556 (70.4%)	65 (65%)	0.27
Outcome variables								
ICU admission	Yes	71 (7.9%)	14 (1.7%)	57 (64%)	< 0.001	10 (1.3%)	61 (59.8%)	< 0.001
	No	830 (92.1%)	798 (98.3%)	32 (36%)		789 (98.7%)	41 (40.2%)	
Recover classification	Totally	42 (5.1%)	42 (5.7%)	-		42 (5.8%)	-	
	Almost	694 (84.1%)	694 (94.3%)	-		681 (94.2%)	13 (12.7%)	
	No	89 (10.8%)	-	89 (100%)		-	89 (87.3%)	
Survival time (days)	Mean ± SD		81.88 ± 0.85			220 ± 2.47		

P values based on chi-square test.

up, the risk of 3.88 and 3.53 for cancer patients were estimated, respectively.

The Bayesian approach was applied for detecting the change-point of age in COVID-19 confirmed patients using different latent distributions (4). As shown in Table 2, given DIC values, model 2 had the best performance at the end of both 30-day and 180-day follow-ups for estimating the threshold of age about 65 years old in cancer patients with confirmed COVID-19. Based on model 2 in Table 2, the odds of cured patients younger than 64 years old were 30 times higher than the older ones. Regarding the considerable difference in cure

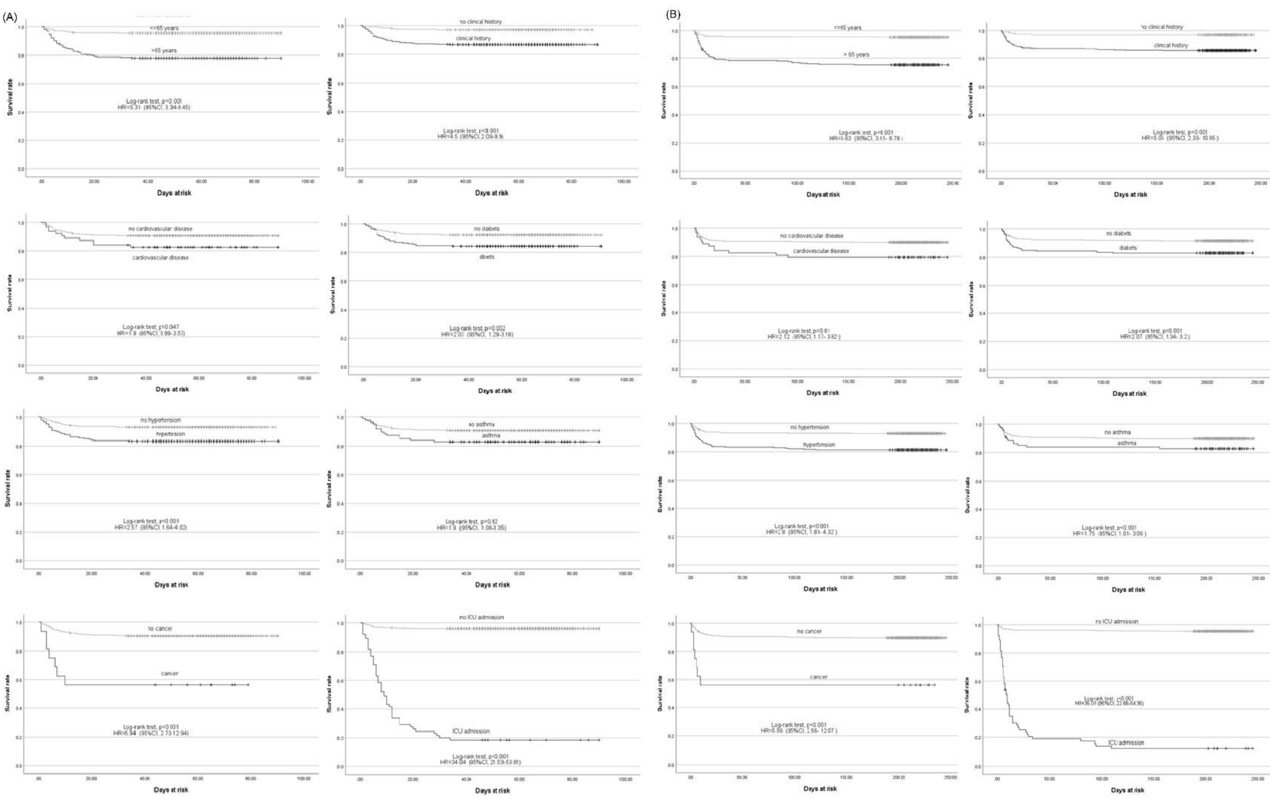

Figure 1. Survival rate in the presence of characteristics associated with death in patients aged > 18 years with confirmed COVID-19. (A): at the end of 30-day follow up, (B): at the end of 180-day follow up

rates between the two age groups, the Bayesian approach provided some shreds of evidence that the age of cancer patients with confirmed COVID-19 might change the cure rate observed in Kaplan-Meier estimations (Figure 1).

Discussion

In the present study, the cumulative incidence of mortality in Iran was around 9% between February 2020 and May 2021. The results of this research demonstrated that elderly patients (>65 years) with comorbidities (cancer) had a higher risk of death according to both Kaplan-Meier survival method and multivariable cox proportional hazards regression model. It was evident from the graphs that almost following a similar pattern, the risk of death did not differ significantly on 30-day and 180-day follow-ups by the passage of time. In addition, using the Bayesian method in the cure rate model with a change-point, threshold of 64 or 65 years old must be considered an important age for outcome prediction of patients with confirmed COVID-19 at the end of two periods of follow-up time.

Many studies indicated the effect of sex on the outcome rate without any clear explanation, but in the present study, the cure rate did not considerably change. Other studies reported that being over 50 or 60 years old with comorbidities except cancer (especially cardiovascular disease) would increase the risk of death, which was not different from the current study results (5-8). In some studies in Iran, the death rate of patients aged over 60 years old increased significantly and the recovery rate of COVID-19 patients aged between 60-69 years old was completely different from the other age categories (9). Moreover, being over 60 years old could increase the odds of death to 12.73 adjusted in multivariable logistic regression through a single center study in Iran (10). In another research in Iran, considering risk factors of developing critical conditions, cancer was reported as the main underlying disease that could increase the risk of death in COVID-19 patients to 4.31 (11). Although the results of other studies were in accordance with findings of this research, none of them considered the survival of cured COVID-19 patients after discharge.

In the current study, 33% of patients who survived had no comorbidities lower than the reported average rate in other studies. In survival analysis, elderly patients with comorbidities, especially cancer, had lower survival rates over follow-up time, which is not similar to what was observed in other studies (12,13). However, relevant findings were observed in the studies carried out in Iran that could confirm the result of this study. According to the aim of the current study, detecting the threshold of age at the end of both 30-day and 180-day follow-ups, 64 years old was estimated by Bayesian method through cure rate model that was in agreement with the other studies in Iran and other countries (7,14-16).

The main limitations of this study were related to the

Table 2. Mixture cure model with threshold of age and the risk of death in patients aged ≥ 18 years old with confirmed COVID-19

Characteristics	β	SE	Exp(β)	95%HPD Interval
At the end of 30-day follow up				
Model 1: Mixture cure model with threshold with exponential latency				
Age (years) ≤ 67				
Patients with cancer	-2.54	0.8	0.09	(-4.09, -0.85)
Age (years) ≤ 67				
Patients with cancer	-1.09	0.76	0.33	(-2.61, -0.3)
Model 2: Mixture cure model with threshold with log-logistic latency				
Age (years) ≤ 64				
Patients with cancer	3.4	3.57	35.5	(1.63, 8.9)
Age (years) > 64				
Patients with cancer	-1.8	0.68	0.16	(-3.15, -0.5)
Model 3: Mixture cure model with threshold with Weibull latency				
Age (years) ≤ 64				
Patients with cancer	3.17	0.62	32.8	(-3.22, 9.53)
Age (years) > 64				
Patients with cancer	-1.65	0.83	0.19	(-2.99, -0.4)
At the end of 180-day follow up				
Model 1: Mixture cure model with threshold with exponential latency				
Age (years) ≤ 62				
Patients with cancer	4.15	3.44	63.43	(-1.34, 9.98)
Age (years) ≤ 62				
Patients with cancer	-1.68	0.63	0.18	(-2.99, -0.49)
Model 2: Mixture cure model with threshold with log-logistic latency				
Age (years) ≤ 62				
Patients with cancer	4.47	3.73	87.36	(1.55, 8.9)
Age (years) > 62				
Patients with cancer	-1.66	0.55	0.19	(-2.75, -0.63)
Model 3: Mixture cure model with threshold with Weibull latency				
Age (years) ≤ 62				
Patients with cancer	1.84	2.5	6.29	(-3.32, 5.39)
Age (years) > 62				
Patients with cancer	-1.56	0.55	0.21	(-2.64, -0.5)

HPD, highest posterior density

patient's responses to clinical history with no further standard test. Moreover, even though missing values of no follow-up records limited the survival via cure model analysis, the results presented in this paper were approximately the same as the world's reported statistics.

Conclusion

It can be seen that COVID-19 mortality was almost similar to regions with a large number of confirmed cases. The current study results indicated that elderly patients with comorbidities had a higher risk of death and shorter survival time. In addition, it was presented that the cure rate would not change remarkably after six months of diagnosis, and fewer deaths would occur in patients older than 64 or 65 years old. Knowing the threshold of age and diseases that might increase the occurrence of death may improve the specialized care needed for its prevention.

Authors' Contribution

Conceptualization: Farimah Shamsi.
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Formal analysis: Farimah Shamsi.
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Investigation: Tahere Fallah Tafti, Yaser Ghelmani.
Methodology: Farimah Shamsi, Yaser Ghelmani.
Project administration: Yaser Ghelmani, Farimah Shamsi.
Resources: Farimah Shamsi, Tahere Fallah Tafti.
Supervision: Yaser Ghelmani.
Validation: Farimah Shamsi.
Visualization: Farimah Shamsi.
Writing–original draft: Farimah Shamsi.
Writing–review & editing: Farimah Shamsi, Yaser Ghelmani, Tahere Fallah Tafti.

Competing Interests

The authors declare no conflict of interests.

Disclaimers

The manuscript and its contents are confidential, intended for journal review purposes only, and not to be further disclosed and the views expressed in this manuscript are our own and not an official position of the institution or funder.

Ethical Approval

This study was approved by the Research Ethics Committee of Shahid Sadoughi University of Medical Sciences and Health Services, Yazd, Iran (Ethics No. IR.SSU.REC.1399.036).

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References

1. Coronavirus Disease (COVID-19): World Health Organization. http://covid19.who.int/. Updated May 29, 2020. Accessed May 31, 2020.
2. Zheng Z, Peng F, Xu B, Zhao J, Liu H, Peng J, et al. Risk factors of critical & mortal COVID-19 cases: a systematic literature review and meta-analysis. J Infect. 2020;81(2):e16-e25. doi: 10.1016/j.jinf.2020.04.021.
3. Chen L, Zhang B, Ti MN, Yang K, Zou Y, Zhang S. Clinical course of severe and critically ill patients with coronavirus disease 2019 (COVID-19): a comparative study. J Infect. 2020;81(2):e82-e4. doi: 10.1016/j.jinf.2020.05.021.
4. Shamsi F, Baghestani AR, Binesh F. Bayesian approach for cure models with a change-point based on covariate threshold: application to breast cancer data. J Biopharm Stat. 2020;30(2):219-30. doi: 10.1080/10543406.2019.1632877.
5. Galbadage T, Peterson BM, Awada J, Buck AS, Ramirez DA, Wilson J, et al. Systematic review and meta-analysis of sex-specific COVID-19 clinical outcomes. Front Med (Lausanne). 2020;7:348. doi: 10.3389/fmed.2020.00348.
6. Nasiri MJ, Haddadi S, Tahvildari A, Farsi Y, Arbabi M, Hasanzadeh S, et al. COVID-19 clinical characteristics, and sex-specific risk of mortality: systematic review and meta-analysis. Front Med (Lausanne). 2020;7:459. doi: 10.3389/fmed.2020.00459.
7. Sousa GJB, Garces TS, Cestari VRF, Florêncio RS,

Moreira TMM, Pereira MLD. Mortality and survival of COVID-19. Epidemiol Infect. 2020;148:e123. doi: 10.1017/s0950268820001405.
8. Salinas-Escudero G, Carrillo-Vega MF, Granados-García V, Martínez-Valverde S, Toledano-Toledano F, Garduño-Espinosa J. A survival analysis of COVID-19 in the Mexican population. BMC Public Health. 2020;20(1):1616. doi: 10.1186/s12889-020-09721-2.
9. Kalantari H, Haji Hossein Tabrizi A, Foroohi F. Determination of COVID-19 prevalence with regards to age range of patients referring to the hospitals located in western Tehran, Iran. Gene Rep. 2020;21:100910. doi: 10.1016/j.genrep.2020.100910.
10. Moradzadeh R, Jamalian SM, Nazari J, Kamali A, Sadeghi B, Hosseinkhani Z, et al. Age-standardized mortality rate and predictors of mortality among COVID-19 patients in Iran. J Educ Health Promot. 2021;10(1):169. doi: 10.4103/jehp.jehp_946_20.
11. Arman A, Tajik M, Nazemipour M, Ahmadinejad Z, Keyvanloo Shahrestanaki S, Hazrati E, et al. Risk factors of developing critical conditions in Iranian patients with COVID-19. Glob Epidemiol. 2021;3:100046. doi: 10.1016/j.gloepi.2020.100046.
12. Shi Y, Yu X, Zhao H, Wang H, Zhao R, Sheng J. Host susceptibility to severe COVID-19 and establishment of a host risk score: findings of 487 cases outside Wuhan. Crit Care. 2020;24(1):108. doi: 10.1186/s13054-020-2833-7.
13. Jordan RE, Adab P, Cheng KK. COVID-19: risk factors for severe disease and death. BMJ. 2020;368:m1198. doi: 10.1136/bmj.m1198.
14. Mirjalili M, Dehghani M, Raadabadi M, Dehghani A. Death risk among COVID-19 patients in Yazd, Iran: a hospital-based case-cohort study. J Mil Med. 2021;23(3):274-82. doi: 10.30491/jmm.23.3.274.
15. Zali A, Gholamzadeh S, Mohammadi G, Azizmohammad Looha M, Akrami F, Zarean E, et al. Baseline characteristics and associated factors of mortality in COVID-19 patients; an analysis of 16000 cases in Tehran, Iran. Arch Acad Emerg Med. 2020;8(1):e70. doi: 10.22037/aaem.v8i1.872.
16. Levin AT, Hanage WP, Owusu-Boaitey N, Cochran KB, Walsh SP, Meyerowitz-Katz G. Assessing the age specificity of infection fatality rates for COVID-19: systematic review, meta-analysis, and public policy implications. Eur J Epidemiol. 2020;35(12):1123-38. doi: 10.1007/s10654-020-00698-1.