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سرویس ترجمه تخصصی



فیلم‌های آموزشی

## کارگاه‌ها و فیلم‌های آموزشی مرکز اطلاعات علمی

آشنایی با پایگاه‌های اطلاعات علمی بین‌المللی و ترندهای جستجو بین‌المللی و ترندهای جستجو

کاربرد نرم افزار SPSS در پژوهش

بروبوزال نویسی (علوم انسانی)

کاربرد نرم‌افزار End Note در استناددهی مقالات و متون علمی

## صدور گواهینامه نمایه مقالات نویسندگان در SID



# 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  $54.93 \pm 17.37$  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 COVID-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 continuous 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



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 20<sup>th</sup> 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 (20<sup>th</sup> November 2020).

### **Statistical analysis**

The paper describes demographic and epidemiological variables using means and standard deviations ( $\pm$ SD), frequency, and percentage (%). The  $\chi^2$  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  $54.93 \pm 7.37$  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 1<sup>st</sup> day, 93% in the 10<sup>th</sup>, and 90% in the 30<sup>th</sup> day of follow-up. Kaplan-Meier survival function at the end of 180-day follow-up time estimated 94% of survival probability in the 40<sup>th</sup> day and 89% in the 180<sup>th</sup> 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

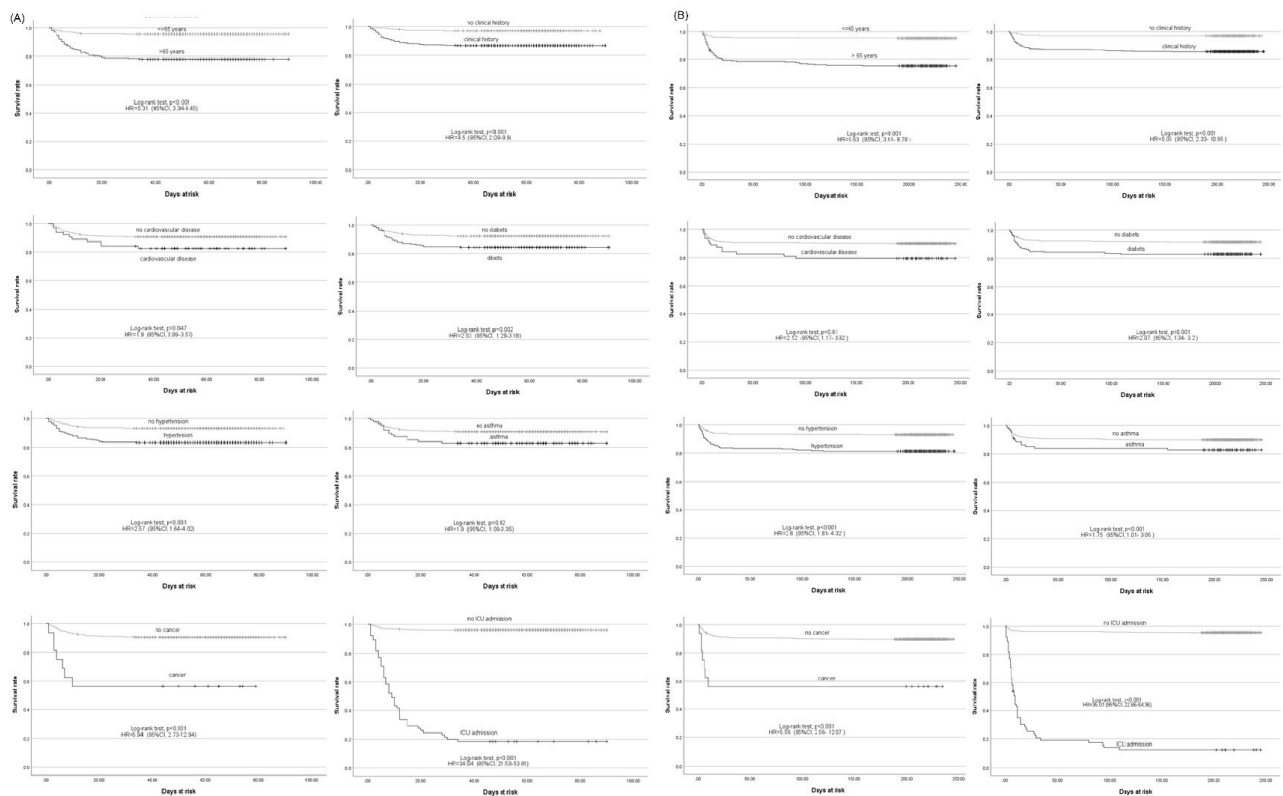
| Variable                 |                 | All population<br>901 (100%) | At the end of 30-day follow-up |                   |         | At the end of 180-day follow-up |                     |         |
|--------------------------|-----------------|------------------------------|--------------------------------|-------------------|---------|---------------------------------|---------------------|---------|
|                          |                 |                              | Survived<br>812 (90.1%)        | Died<br>89 (9.9%) | P value | Survived<br>99 (88.7%)          | Died<br>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    |
| <b>Outcome variables</b> |                 |                              |                                |                   |         |                                 |                     |         |
| 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  $\geq 18$  years old with confirmed COVID-19

| Characteristics  | $\beta$ | SE   | Exp( $\beta$ ) | 95%HPD Interval |
|--|---------|------|----------------|-----------------|
| <b>At the end of 30-day follow up</b>                                |         |      |                |                 |
| Model 1: Mixture cure model with threshold with exponential latency  |         |      |                |                 |
| Age (years) $\leq 67$  |         |      |                |                 |
| 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) $\leq 64$  |         |      |                |                 |
| 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) $\leq 64$  |         |      |                |                 |
| 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)   |
| <b>At the end of 180-day follow up</b>                               |         |      |                |                 |
| Model 1: Mixture cure model with threshold with exponential latency  |         |      |                |                 |
| Age (years) $\leq 62$  |         |      |                |                 |
| Patients with cancer   | 4.15    | 3.44 | 63.43          | (-1.34, 9.98)   |
| Age (years) $\leq 62$  |         |      |                |                 |
| 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) $\leq 62$  |         |      |                |                 |
| 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) $\leq 62$  |         |      |                |                 |
| 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**

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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.  
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**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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# SID



بلاگ مرکز اطلاعات علمی



کارگاه‌های آموزشی



سرویس ترجمه تخصصی



فیلم‌های آموزشی

## کارگاه‌ها و فیلم‌های آموزشی مرکز اطلاعات علمی

آشنایی با پایگاه‌های اطلاعات علمی بین‌المللی و ترندهای جستجو بین‌المللی و ترندهای جستجو

کاربرد نرم افزار SPSS در پژوهش

بروبوزال نویسی (علوم انسانی)

کاربرد نرم‌افزار End Note در استناددهی مقالات و متون علمی

## صدور گواهینامه نمایه مقالات نویسندگان در SID