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Tocilizumab in ICU-admitted COVID-19 Patients: A Retrospective Study

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Abstract

Background: Severe and critically-ill COVID-19 patients are characterized by a severe inflammatory response. Pharmacologic inhibition of acute-phase inflammatory pathways such as IL-6 receptor inhibitor, Tocilizumab (TCZ) may improve patient outcomes in these cases. Consequently, the therapeutic benefit of TCZ was evaluated in this study.

Methods: We evaluated intravenous tocilizumab in severe and critically ill adult COVID-19 patients who met pre-defined stringent CRS criteria. A single-center, prospective, observational cohort study was carried out among consecutive adult (≥18 years of age) in-patients with COVID-19 between March 20, 2020 and March 20, 2021. In total, 354 patients were included in our study. Mortality and time to hospital discharge were compared between patients who received tocilizumab treatment (n = 177) and those who did not (n = 177).

Results: A total of 354 patients were analyzed whereas 177 patients were included in each group. In those receiving TCZ, all-cause mortality was significantly reduced, corresponding to an adjusted hazard ratio (HR) of 0.57, (95% confidence interval (CI): 0.43-0.76; $P < 0.001$). Furthermore, time to discharge was significantly improved in the TCZ group (HR: 1.66; 95%CI: 1.17-2.36, $P = 0.004$). Invasive mechanical ventilation was not statistically different among the study groups after adjusting for confounding variables (HR: 1.38; 95%CI: 0.89-2.14; $P = 0.139$). Dosing frequency was independent of survival status ($P = 0.676$).

Conclusion: The use of TCZ in ICU-hospitalized patients resulted in improved patient survival and reduced duration of hospitalization. Further studies are needed to confirm the efficacy of TCZ in severe and critical COVID-19 cases.

Keywords: COVID-19, SARS-CoV-2 virus, IL-6 Receptor Inhibitor, Tocilizumab, Intensive Care Unit

Conflicts of Interest: *None declared*
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Introduction

The worldwide outbreak of COVID-19 caused the death of more than 6 million individuals around the world, since emerging in late 2019 ("WHO Coronavirus Disease (COVID-19) Dashboard,").

While the preventive measures, including vaccines and certain pharmacological agents such as dexamethasone, have significantly reduced the morbidity and mortality caused by the virus (1-3), Apart from support management for continuous infection, there is no definitive treatment. Although, most COVID-19 patients with mild symptoms within weeks, in severe and critical cases of the disease which occur in 14% to 5% of the patients, individuals may present with symptoms of pneumonia, respiratory failure, and acute respiratory distress syndrome, hypercoagulability, and septic shock requiring hospitalization and invasive mechanical ventilation (4). The pathophysiology of severe infections is characterized by a cytokine storm caused by dysregulated pro-inflammatory cytokines production such

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↑What is "already known" in this topic:
Coronavirus Disease 2019 (COVID-19) has become a worldwide pandemic and is a threat to global health. Patients who experienced cytokine storms tend to have a high mortality rate. This was the first study to investigate the impact of tocilizumab in patients admitted in ICU in Iran.

→What this article adds:
The results of this study showed that the administration of TCZ reduces mortality by preventing end-organ damage and the need for advanced life support.

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as IFN-γ, TNF and IL-6 (5). Consistent with the concept of administering dexamethasone to reduce mortality, research has focused on more targeted anti-inflammatory drug approaches in COVID-19. Indeed, pathogenic T cells and monocytes secreting IL-6 are implicated in inciting the inflammatory storm in COVID-19 (6). Furthermore, IL-6 has been associated with the severity of COVID-19, exacerbation of ARDS, and the likelihood of invasive ventilation (5). IL-6 may also contribute to the pathophysiology of the disease by modulating vascular permeability and endothelial function (7).

Therefore, tocilizumab (TCZ), a monoclonal antibody against the IL-6 receptor approved for use in patients with T-cell-induced cytokine release syndrome, is a promising agent to reduce mortality and improve treatment outcomes (5). While TCZ has been initially shown in a number of preceding studies to improve patient outcomes (8), the more recent studies of TCZ have demonstrated mixed results (9, 10), which could be recognized in the dual role of IL-6 signaling and its greater potential benefit in cases with severe inflammation (11-13). Therefore, in this retrospective observational study, we aimed to evaluate the therapeutic benefit of TCZ on overall mortality, invasive mechanical ventilation rate, and length of stay in severe and critically ill COVID-19 patients.

Methods

Study design and samples

This single-center retrospective comparative study was conducted on data from the intensive care unit of Imam Ali Hospital in Alborz Province, Iran, from March 20, 2020, to March 20, 2021. Inclusion criteria were 18 years of age and older who were hospitalized in the intensive care unit (ICU), those patients had either positive polymerase chain reaction (PCR) test for SARS-CoV-2 virus from nasopharyngeal samples or the presence of pulmonary abnormalities in high resolution computed tomography scan suggestive of respiratory COVID-19, showing symptoms of cytokine release syndrome (CRS; defined further below according to the hospital guidelines) within 3 days of hospitalization in ICU. Exclusion criteria were patients with incomplete medical records or those lost to follow-up. Written informed consent was obtained from all the participants. Patients were followed from admission to ICU until discharge from the hospital or death, whichever happened. The hospital followed the daily visit of attending physicians. Daily follow-up continued until the Patients' death or hospital discharge. This study was approved by the Institutional review board at Alborz University of Medical Sciences (Approval ID: 4126-82). Ethical approval was granted by the Alborz Medical College Ethics Committee (Approval ID: IR.ABZUMS.REC.1400.041).

Patients were divided into those receiving at least one dose of TCZ (TCZ group) plus standard of care and those receiving standard of care (non-TCZ group). All patient records eligible were randomly selected for each group to be included in the study with a 1:1 enrollment ratio.

A COVID-19 case was wrapped up by realizing the following criteria by cytokine storm: peripheral capillary oxygen saturation (SpO_2) < 90% on at least 4 L of oxygen OR deteriorating hypoxemia PLUS 1 or more of the following predictors for severe disease: serum IL-6 level ≥7 pg/ml and C-reactive protein level >75 mg/L. hypoxemia deterioration was considered as a new rise in patient oxygen need that needed support by nasal cannula, Venturi or noninvasive masking, or invasive mechanical ventilation.

Data collection

The related data of patients were collected manually from hospital records and written charts, and anonymously transferred to a standardized form by study physicians. Collected data were: 1) age and gender; 2) comorbidities; 3) Number of TCZ doses received 4) need for intensive mechanical ventilation (IMV); 5) intubation prior to or after receiving TCZ in TCZ group; 6) length of stay in ICU; 7) antimicrobial and other immunomodulatory therapies and supportive care; 8) C-reactive protein (CRP) and ferritin on day of diagnosis CRS; 9) Clinical outcomes at the end of the follow-up period including patient mortality, and duration of hospitalization.

Patient comorbidities, including diabetes mellitus (DM), hypertension (HTN), chronic kidney disease (CKD) and cardiovascular disease (CD) were documented for each patient as well. Comorbidity was initially treated as a categorical variable (yes or no) and then classified based on the absolute number of them with one, two or more than or equal to three comorbidities.

Treatment and Observation

The standard of care included remdesivir (200 mg IV on the first day, and 100 mg IV on subsequent days, for a minimum of 5 days), dexamethasone (8 mg IV), Unfractionated heparin (5000U SC) every 8 hours, oxygen therapy or respiratory support, intravenous fluid replacement, as well as, antipyretics and bronchodilator drugs. If the cytokine storm was suspected upon admission to the ICU or within 72 hours, according to the definition in describing the hospital COVID-19 treatment protocol, the decision to administer TCZ was made at the treating physician's discretion and patient's consent. TCZ was administered at a dose of 400mg as an intravenous infusion over 1 hour that could be repeated up to 2 additional times over the hospitalization period if clinical symptoms worsened or showed no improvement. Comorbidities were determined based on the patients' self-reports at admission. All-cause mortality from the start of hospitalization, defined as time to death endpoint starting from the admission to ICU, rate of invasive mechanical ventilation throughout their stay and duration of hospitalization in discharged patients were used to assess drug efficacy.

Statistical analyses

Demographic, clinical, and laboratory data in the study groups were summarized using descriptive statistics, mean (standard deviation (SD)) or median (interquartile range (IQR)) for continuous variables and frequency (percentage) for categorical variables. Characteristics of TCZ and non-TCZ groups as well as survivors and non-survivors in

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the TCZ group, were compared using two-tailed t-tests, Mann–Whitney U tests, Fisher exact, or chi-square tests, as appropriate.

All-cause mortality was analyzed by time-to-event analysis with Cox proportional odds model in univariate and multivariate analyses to obtain crude and adjusted Hazard Ratios (HRs) and 95% confidence intervals (CI). A backward likelihood ratio selection approach was used to include covariates in the adjusted model. Kaplan-Meier curves were used to reveal cumulative survival in patients in each study arm. The same method was utilized to compare time to discharge in patients discharged from the hospital in each group. The use of invasive mechanical ventilation in patients was assessed using a binary logistic regression model adjusted for covariates using a backward likelihood ratio selection approach.

Statistical significance was defined as a two-tailed P value < 0.05. Statistical analyses were performed using SPSS Version 26.0 (SPSS Chicago, IL, USA) and Stata Version 17.

Results

A total of 354 severe and critically-ill COVID-19 patients were included in the study, 177 of whom received at least one dose of TCZ (TCZ group). Patient demographics and clinical characteristics at baseline are shown in Table 1.

The TCZ group was comprised of 88 (49.7%) men and 89 (50.2%) women with an average age of (Mean±SD) 59.2±13.4 years. The non-TCZ group consisted of 84 (47.4%) men and 93 (52.5%) women with an average age of 61.3±13.2. in the TCZ group, patients with comorbidities included 44 (24.9%) diabetics, 70 (39.5%) patients with hypertension, 12 (6.8%) patients with chronic kidney disease, and 9 (5.1%) patients with coexisting cardiovascular diseases. The non-TCZ group included 62 (35.0%) diabetics, 63 (35.6%) patients with hypertension, 13 (7.3%) patients with chronic kidney disease and 6 (3.4%) patients with cardiovascular diseases. Median (IQR) serum CRP and ferritin levels in the TCZ group vs. non-TCZ group were 118 (79.9-172.4) vs. 130.2 (93.5-171.4) and 639 (376.5-893.3) vs. 574.8 (332.0-897.2), respectively. There was no statistically significant difference between the TCZ and non-TCZ groups in the number of comorbidities (total $P = 0.662$).

In the TCZ group, non-survivors were significantly older compared to those discharged 61.8±13.0 vs. 56.6±13.3; P-value = 0.009). The frequency of the comorbidities of DM, HTN, CKD and CD were similar between survivors and non-survivors. There was no statistically significant difference between the survivors and non-survivors in CRP 124 (84.0-165.2) vs. 109 (78.4-186.2) and ferritin levels 653.0 (409.5-987.0) vs. 627.4 (357.6-842.7). Duration of hospitalization from admission to ICU transfer was shorter in non-survivors compared to survivors (mean (SD) 1.9 (1.7) vs. 2.3 (1.4) $P = 0.033$). In the TCZ group, 8% of the patients received a single dose of TCZ, 72.9% of the patients received two doses of TCZ, and 18.6% of the patients received three doses of TCZ at the discretion of the attending physician. No difference was observed in the number of administered TCZ doses in survivors compared to non-survivors ($P = 0.676$) (Table 2).

Table 1. Baseline patient characteristics and disease outcomes

Variables	Tocilizumab (N = 177)	Non-Tocilizumab (N = 177)	*P*-value
Demographics			
Age (year), mean (SD)	59.2 (13.4)	61.2 (13.2)	0.151
Age ≥ 65 year, N (%)	63 (35.6%)	72 (40.7%)	0.381
Gender, male, N (%)	88 (50.0%)	84 (47.7%)	0.749
Days from hospitalization to ICU admission, mean (SD)	2.1 (1.6)	2.3 (1.8)	0.267
Comorbidities, N (%)			
DM	44 (24.9%)	62 (35%)	0.048
HTN	70 (39.5%)	63 (35.6%)	0.510
CKD	12 (6.8%)	13 (7.3%)	1.000
CD	9 (5.1%)	6 (3.4%)	0.599
Number of Comorbidities, N (%)			
0	90 (50.8%)	89 (50.3%)	0.662
1	50 (28.2%)	43 (24.3%)	
2	26 (14.7%)	34 (19.2%)	
≥ 3	11 (6.2%)	11 (6.2%)	
Inflammation markers, median (IQR)			
C-reactive protein level (mg/L)	118 (79.9-172.4)	130.2 (93.5-171.4)	0.047
Ferritin serum level (µg/L)	639 (376.5-893.3)	574.8 (332.0-897.2)	0.258
Overall mortality, N (%)	89 (50.3%)	125 (70.6%)	<0.001
ICU length of stay in discharged patients, mean (SD)	10.2 (5.1)	13.3 (3.7)	<0.001
Invasive mechanical ventilation, N (%)	98 (55.4%)	81 (45.8%)	0.071
Total duration of hospitalization in discharged patients, mean (SD)	14.9 (5.3)	18.6 (4.5)	<0.001

DM diabetes mellitus, HTN Hypertension, CKD Chronic kidney disease, CD Cardiovascular disease, SD Standard deviation, IQR Interquartile range, ICU Intensive care unit

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Table 2. Distribution of study variables between discharged and dead patients in those receiving Tocilizumab.

Variables	Discharged (N = 88)	Died (N = 89)	*P*-value
Demographics			
Age (year), mean (SD)	56.6 (13.3)	61.8 (13.3)	0.009
Age ≥ 65 year, N (%)	23 (26.1%)	40 (44.9%)	0.012
Gender male, N (%)	47 (53.4%)	41 (46.6%)	0.451
Comorbidities, N (%)			
DM	22 (25.0%)	22 (24.7%)	1.000
HTN	36 (40.9%)	34 (38.2%)	0.760
CKD	5 (5.7%)	7 (7.9%)	0.766
CD	4 (4.5%)	5 (5.6%)	0.745
Number of Comorbidities, N (%)			
0	43 (48.9%)	47 (52.8%)	
1	26 (29.5%)	24 (27.0%)	
2	16 (18.2%)	10 (11.0%)	0.267
≥ 3	3 (3.4%)	8 (9.0%)	
Inflammation markers, median (IQR)			
C-reactive protein level	109 (78.4-186.2)	124 (84.0-165.2)	0.759
Ferritin serum level	627.4 (357.6-842.7)	653.0 (409.5-987.0)	0.241
Number of doses received, N (%)			
1	6 (6.8%)	9 (10.1%)	
2	64 (72.7%)	65 (73.0%)	0.676
3	18 (20.5%)	15 (16.9%)	
Days from hospitalization to ICU admission, mean (SD)	2.3 (1.4)	1.9 (1.7)	0.033
Tocilizumab administration time relative to intubation, N (percentage in each comparison)			
Prior to intubation	4 (12.9%)	27 (87.1%)	0.194
After intubation	17 (25.4%)	50 (74.6%)	

DM diabetes mellitus, HTN Hypertension, CKD Chronic kidney disease, CD Cardiovascular disease, SD Standard deviation, IQR Interquartile range, ICU Intensive care unit

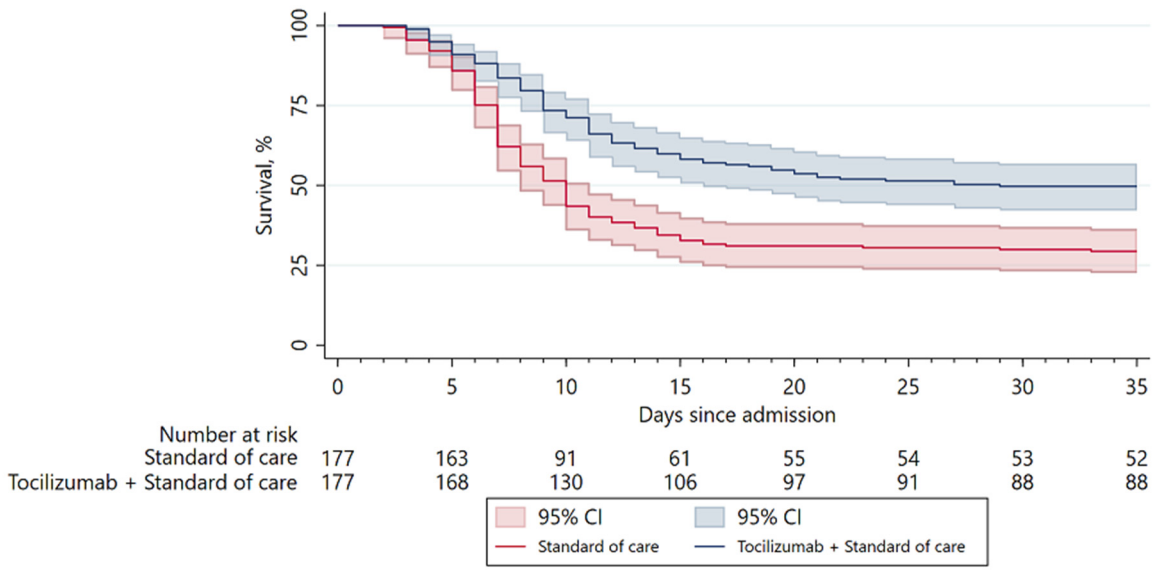

Figure 1. Kaplan-Meier survival function curve for cumulative survival. A significant improvement in patient survival in overall mortality was observed in those receiving Tocilizumab, analyzed using an adjusted Cox regression proportional odds model.

All-cause mortality occurred in 89 patients (50.3%) receiving TCZ and in 125 patients not receiving the drug (70.6%). The mean time from hospitalization to ICU admission was 2.1±1.6 days for the TCZ group and 2.3±1.8 days for non-TCZ patients. The cumulative survival of the patients in each study group is demonstrated using a Kaplan-Meier curve in Figure 1. The analysis revealed significantly higher survival rates in the TCZ group, corresponding to a hazard ratio (HR) of 0.57 (95% CI: 0.43-0.76; $P < 0.001$). The hazard ratio was adjusted for age, sex, and coexisting chronic kidney disease (Table 3).

The number of patients requiring invasive mechanical ventilation was 98 (55.4%) patients in the TCZ group and 81 (45.8%) patients in the non-TCZ group, corresponding to an odds ratio of 1.38 (95% CI :0.89 to 2.14; $P = 0.139$) adjusted for ferritin levels, and patient history of diabetes, chronic kidney disease, and cardiovascular diseases in patients. their results did not show a significant change in terms of mechanical ventilation rate in those receiving TCZ (Table 3).

In those discharged following hospitalization, ICU length of stay was significantly lower in those receiving

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Table 3. Statistical analysis of overall mortality, invasive mechanical ventilation rate, and time to discharge of the included participants

Clinical outcome		Tocilizumab (N = 177)	Non-Tocilizumab (N = 177)	Univariate model		Adjusted model	
				Crude estimate	*P*	Adjusted estimate	*P*
All-cause mortality (Time to death from ICU admission), N (%)	No	88 (49.7%)	52 (29.4%)	0.57 (0.43 to 0.758)[$]	<0.001	0.57 (0.43 to 0.76)[a]	<0.001
	Yes	89 (50.3%)	125 (70.6%)				
Invasive mechanical ventilation, N (%)	No	79 (44.6%)	96 (54.2%)	1.4 (0.96 to 2.23)[#]	0.071	1.38 (0.89 to 2.14)[b]	0.139
	Yes	98 (55.4%)	81 (45.8%)				
Time to discharge (total duration of hospitalization), days (Mean ± SD)		14.9±5.3	18.5±4.5	1.66 (1.17 to 2.36) [$,e]	0.004	-	-

*: Data presented as number (%); $: hazard ratio; #: odd ratio; SD: standard deviation; CKD: Chronic kidney disease; CD: Cardiovascular disease; DM: Diabetes mellitus;

[a]: Hazard ratio calculated using Multiple Cox Regression, adjusted for age, sex, and CKD prevalence.

[b]: Odds ratio derived from a Multiple Logistic Regression model, adjusted for serum ferritin, and DM, CKD, and CD prevalence

[e]: Hazard ratio calculated using univariate Cox Regression.

TCZ (10.3±5.2) compared to the non-TCZ group (13.4±3.8). Furthermore, the time interval from the ICU admission to discharge from the hospital in TCZ and non-TCZ groups was 12.6±5.5 vs. 16.5±4.3, respectively. The mean duration of hospitalization starting from admission in to the hospital to discharge was 14.9±5.3 days in the TCZ group compared to 18.6±4.5 days in the non-TCZ group, corresponding to an HR of 1.66 (95% CI: 1.17 to 2.36; $P = 0.004$).

Discussion

The results of this study showed that considerably higher survival rate and lower duration of hospitalization in patients receiving TCZ in addition to standard of care compared to standard of care alone. This study adds to the literature pertaining to the healing benefit of IL-6 receptor inhibitors in severe and critically-ill COVID-19 patients.

The results of our study may recommend that the early administration (within 72 hours of ICU admission) of TCZ decreases mortality by preventing end-organ damage and the need for progressive life support. While we did not observe significantly lower rates of invasive mechanical ventilation in the TCZ group (55.4% vs. 44.8%) or improved survival in the subset of patients receiving at least a single dose of TCZ prior to intubation and mechanical ventilation related to those intubated in the non-TCZ group (12.9% vs. 13.6%, data not shown), the mortality rate was meaningfully lower in patients receiving TCZ with non-invasive ventilation compared to non-TCZ patients with same respiratory status (84.8% vs 42.7%, data not shown). As such, it is reasonable to assume that TCZ would be most useful for patients prior to the onset of significant organ damage or clinical deterioration in ICU settings.

The justification to use TCZ in COVID-19 in our study center was premised on the understanding that dysregulation of the immune system plays a crucial role in the clinical course of severe and critical COVID-19 (14), also supported by the findings that anti-inflammatory effects of systemic corticosteroids were beneficial among hospitalized COVID-19 patients requiring oxygen support (2). Interventions targeting the pro-inflammatory immune response could potentially help decrease excess cytokine production and release. Initial reports showed that high levels of inflammatory cytokines (mainly IL-1b, IL-6, IL-10, IFN-γ, IP-10, and MCP-1) in COVID-19 patients are associated with more severe disease, pulmonary inflammation, and multiple organ failure (15, 16). Most notably, IL-6 seems to play a crucial role, as in COVID-19, increased serum levels have been correlated with unfavorable outcomes such as respiratory failure, acute respiratory distress syndrome (ARDS) and death (17, 18). Pre-COVID-19 investigations focused on cytokine release syndrome and secondary hemophagocytic lymph histiocytosis, which have similar pathophysiology, established the effectiveness of IL-6 and IL-6R antagonists in these conditions (13, 19). Case reports and small observational studies revealed that interventions targeting IL-6 signaling pathways, such as TCZ, might rectify the dysregulated immune COVID-19 patients resulting in improved outcomes, such as lower risk mortality risk or the need for mechanical ventilation (20-23). These studies, however, were limited by small sample size, lack of control group, or absence of adjusted analyses. It should be noted that dosing and criteria for tocilizumab administration were used differently and did not adhere to a uniform CRS definition, resulting in diverse and hardly comparable participants and results in the studies (24, 25). However, a recent large randomized study reported that administering TCZ in combination with systemic corticosteroids resulted in considerably lower mortality in patients using oxygen support with elevated C-reactive protein levels (>75 mg/L) (26). This observation supports the hypothesis that blocking IL-6 signaling may only be favorable in the presence of CRS in patients who received TCZ. It is of note to say that supply of the number of TCZ doses between survivors and non-survivors was not statistically different in this study on severe and critical COVID-19 patients.

Conclusion

Analysis of 354 patient outcomes in this study demonstrated that the use of TCZ was associated with lower length of ICU stay and total duration of hospitalization, as well as better survival outcomes in severe and critically-ill COVID-19 patients with high serum inflammation markers after adjustment for potential confounding baseline variables. Despite inconsistent results in previous randomized clinical trials, the growing body of evidence supporting the efficacy of TCZ should be considered.

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Contribution of Author

MH-Y and ZS conceptualized the present study, acquired data from the hospital registry and edited the manuscript. PK extracted anonymized patient data. PK and SA wrote the manuscript. SA conducted the statistical analysis.

Ethical approval

Ethical approval was granted by the ethics committee at Alborz University of Medical Sciences (Approval ID: IR.ABZUMS.REC.1400.041).

Conflict of Interests

The authors declare that they have no competing interests.

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