# The significant impact of Coronavirus disease 2019 (COVID-19) on in-hospital mortality of elderly patients with moderate to severe traumatic brain injury: A retrospective observational study

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## ARTICLE INFO

## ABSTRACT

Background: Traumatic brain injury (TBI) is one of the main causes of death and disability among the elderly patient population. This study aimed to assess the predictors of in-hospital mortality of elderly patients with moderate to severe TBI who presented during the Coronavirus disease 2019 (COVID-19) pandemic.

Methods: In this retrospective analytical study, all elderly patients with moderate to severe TBI who were referred to our center between March 2nd, 2020 to August 1st, 2020 were investigated and compared against the TBI patients receiving treatment during the same time period within the year 2019. Patients were followed until discharge from the hospital or death. The demographic, clinical, radiological, and laboratory test data were evaluated. Data were analyzed using SPSS-21 software.

Findings: In this study, 359 elderly patients were evaluated (n = 162, Post-COVID-19). Fifty-four patients of the cohort had COVID-19 disease with a mortality rate was 33.3%. The patients with COVID-19 were 5.45 times more likely to expire before discharge (P < 0.001) than the TBI patients who were not COVID-19 positive. Other variables such as hypotension (OR, 4.57P < 0.001), hyperglycemia (OR, 2.39, P = 0.002), and use of anticoagulant drugs (OR, 2.41P = 0.001) were also associated with in-hospital death. According to the binary logistic regression analysis Age (OR, 1.72; 95% CI: 1.26–2.18; P = 0.033), Coronavirus infection (OR, 2.21; 95% CI: 1.83–2.92; P = 0.011) and Glasgow Coma Scale (GCS) (OR, 3.11; 95% CI: 2.12–4.53; P < 0.001) were independent risk factors correlated with increased risk of in-hospital mortality of elderly patients with moderate to severe TBI.

Conclusion: Our results showed that Coronavirus infection could increase the risk of in-hospital mortality of elderly patients with moderate to severe TBI significantly.

## 1. Introduction

Traumatic brain injury (TBI) is one of the main causes of death and disability, particularly in the elderly patient population [1].

Along with the significant growth in the 65 and older patient population, we have also observed an increase in the number of elderly patients with TBI [2]. Acknowledging the long-term disability and socioeconomic cost of TBI, thorough knowledge of proper management, and improvement in the ability to predict the patient outcomes will confer enormous benefit in years to come.

The novel Sars-Cov-2 virus has left the scientific community with a deficit of acumen and predictive knowledge of outcomes in the affected patients. The Coronavirus disease 2019

(COVID-19) emerged from Wuhan, China and was classified as a pandemic by the World Health Organization on March 11, 2020 [3]. The first reported cases in Iran were confirmed in Qum on February 18, 2020. Since its advent, COVID-19 has negatively impacted the healthcare workers' ability to control the spread of the infection, ration resources, and manage the increased patient volume. COVID-19 has impacted multiple arenas including the neurosurgical workforce [4]. This study has two aims: first to assess predictors of in-hospital mortality in elderly patients with TBI during the COVID-19 pandemic and secondly to investigate the impact of COVID-19 on in-hospital mortality of TBI patients 65 and older.

## 2. Methods

### 2.1. Design

In this retrospective analytical study, all elderly patients (age 65 years and older) with moderate to severe TBI according to the Head Injury Severity Scale classification) who were referred to our center between March 2nd, 2020 to August 1st, 2020 were investigated and compared against the TBI patients receiving treatment during the same time period within the year 2019 [5]. The demographic, clinical, radiological, and laboratory test data were evaluated. Initial head computed tomography scans (CT) were classified retrospectively according to the Rotterdam Classification [6,7].

### 2.2. Aim 1 study period

To assess for predictors of in-hospital mortality within the first aim of the study, admission and treatment period was during March 2nd, 2020 to August 1st, 2020.

### 2.3. Aim 2 study periods

To assess in-hospital mortality in COVID-19 patients, medical records of enrolled patients from March 2nd, 2020 to August 1st, 2020 (after the first case in Iran i.e. Post-COVID-19) were compared against those of the same period the year prior (March 2nd, 2020 to August 1st, 2019, i.e. Pre-COVID-19).

### 2.4. Management and outcomes

All patients were treated according to the Advanced Trauma Life Support guidelines for Management of Severe Head Injury where mass lesions were surgically evacuated and all unconscious patients of a GSC $\leq$ 8 were intubated and mechanically ventilated [8]. Infection with SARS-CoV-2 was confirmed by nucleic acid-based polymerase chain reaction (PCR) and/or a positive chest high-resolution CT (HRCT) examination within 48 h after admission. The analysis of COVID vs non-COVID was based on admission COVID status.

Clinical outcome was evaluated at the time of hospital discharge using the Glasgow Outcome Scale (GOS) [9]. The GOS measures global functioning with five outcome categories: [1] death, [2] persistent vegetative state, [3] severe disability (conscious but dependent on others for daily activities), [4] moderate disability (disabled but independent in daily activities), and [5] good recovery (normal life resumed, with minor neurological deficits possible). In this study, the GOS groups were classified in binary categories: surveyed at discharge and death.

### 2.5. Study approval

The study was approved by the Institutional Review Board and Ethics Committee of the Kermanshah University of Medical Science, according to the Declaration of Helsinki in its present form. The STROBE statement checklist for cohort studies was used as a reporting guideline.

### 2.6. Statistical analysis

Differential and inferential statistical analyses were conducted utilizing IBM SPSS Statistics [version 21] (IBM Corp., Armonk New York, USA). Variables were described using the frequency, frequency percentage, mean and standard deviation (SD). To assess for normal distribution of continuous data the Kolmogorov-Smirnov test was used. Non-parametric qualitative analysis was done utilizing the Mann-Whitney $U$ test, specifically for age, GCS, and Rotterdam score. The distribution of the qualitative variables and patient status was evaluated with a chi-squared test where the odd Ratio was also reported. The multivariable logistic regression model was used to assess the association between the outcome and potential risk factors. The significance level for the analytical tests was <0.05.

## 3. Results

### 3.1. Aim 1: Predictors of in-hospital mortality during COVID-19 pandemic

A total of 162 patients met the inclusion criteria (55.5% male) over the 5-month study period. No patients were excluded and intracranial surgery was performed on 61 patients (37.7%) due to increased intracranial pressure refractory to medical management. The mean age at trauma was 72.98 (SD = 5.22) and 69.66 (SD = 4.01) for COVID positive and negative patients, respectively. The mean GCS on admission was 7.33 (SD = 1.41) and 8.01 (SD = 1.91) for COVID-19 positive and negative patients, respectively. Also, the mean length of hospital stays 21.14 (SD = 3.19) and 11.03 (SD = 4.28) for COVID-19 positive and negative patients, respectively [Table 1]. Fifty-four (33.3%) patients were confirmed to be COVID-19 positive with a mortality rate of 55.5% while the overall in-hospital mortality rate was 25.3% for all study patients admitted during the pandemic period [Table 2].

The mean age for patients surveyed at discharge was 69.28 (SD = 3.57) and the mean age for patients who died was 75.14 (SD = 4.94) (P < 0.001). Patients surveyed at discharge had an average GCS of 8.25 (SD = 2.11) compared to 4.94 (SD = 5.63) for patients who died (P < 0.001). However, the hospital stays of these patients were longer than those who died at 18.78 (SD = 3.22) and 13.3 (SD = 2.8), respectively (P < 0.041). [Table 3].

**Table 1**
Relationship between COVID-19 status and quantitative variables.

| Variable | COVID-19 PositiveMean (SD) | COVID-19 Negative Mean (SD) | Statistical test |
|---|---|---|---|
| Age (Year) | 72.98 (5.22) | 69.66 (4.01) | **P < 0.001*** |
| GCS | 7.33 (1.41) | 8.01 (1.91) | P = 0.212 |
| Hospital stay (day) | 21.14(3.19) | 11.03 (4.28) | **P = 0.012*** |
| WBC | 8721 (2132) | 7563 (3421) | P = 0.601 |
| Platelet count | 198,765 (73962) | 202,141 (99519) | P = 0.765 |
| PT | 14.33 (1.39) | 14.76 (1.26) | P = 0.441 |
| PTT | 31.11 (2.30) | 32.06 (3.22) | P = 0.521 |

GCS: Glasgow Coma Score, PT: Prothrombin Time, PTT: Partial Thromboplastin Time
(*) means p < 0.05

**Table 2**
Pre- and Post-COVID-19 Infection and Mortality Rate.

| | Pre-COVID-19 | Post-COVID-19 | Statistical Test |
|---|---|---|---|
| All patients | 197 (54.9%) | 162 (45.1%) | |
| In-hospital mortality | 32 (16.24%) | 41 (25.3%) | P = 0.034 |
| COVID19 Infections | – | 54 (33.3%) | |

Pre-COVID-19: March 2nd – August 1ªt 2019, Post-COVID-19: March 2nd – August 1st 2020

**Table 3**
Binary Logistic Regression Analysis.

| Variables | Odds ratio | 95% CI | P value |
|---|---|---|---|
| Age | 1.72 | 1.26–2.18 | **P = 0.010** |
| Coronavirus infection | 2.21 | 1.83–2.92 | ***P = 0.011** |
| GCS | 3.11 | 2.12–4.53 | ***P < 0.001** |
| Rotterdam score | 1.47 | 0.89–1.73 | P = 0.231 |
| Anticoagulant drugs | 1.31 | 0.96 – 2.34 | P = 0.343 |

Numerous variables were associated with an increased risk of in-hospital mortality: hyperglycemia (odds ratio [OR],2.39, P = 0.002), hypotension (OR, 4.57, P < 0.001), use of anticoagulant medication (OR,2.41; P = 0.001), and Rotterdam Score (P < 0.001). Positive infection with COVID-19 was most strongly correlated with an increased risk of in-hospital mortality (OR, 5.45, P < 0.001) [Table 4].

There was no significant relationship between COVID-19 status and GCS (P = 0.212). According to the binary logistic regression analysis Age (OR, 1.72; 95% CI: 1.26–2.18; P = 0.033), Coronavirus infection (OR, 2.21; 95% CI: 1.83–2.92; P = 0.011) and Glasgow Coma Scale (GCS) (OR, 3.11; 95% CI: 2.12–4.53; P < 0.001) were independent risk factors correlated with increased risk of in-hospital mortality of elderly patients with moderate to severe TBI [Table 5].

**Table 5**
Relationship between in-hospital mortality and quantitative variables.

| Variable | In hospital mortality | | Statistical test |
|---|---|---|---|
| | YES | NO | |
| Age (Year) | 75.14(4.94) | 69.28 (3.57) | P < 0.001* |
| GCS | 5.63 (0.97) | 8.25 (2.11) | P < 0.001* |
| Hospital stay (day) | 13.3(2.89) | 18.78 (3.22) | P = 0.041* |
| WBC | 8312 (1821) | 7865 (2321) | P = 0.564 |
| Platelet count | 176555 (63721) | 199879 (89423) | P = 0.631 |
| PT | 14.12 (1.28) | 14.63 (1.23) | P = 0.213 |
| PTT | 31.27 (2.34) | 32.17 (3.06) | P = 0.489 |

GCS: Glasgow Coma Score, PT: Prothrombin Time, PTT: Partial Thromboplastin Time.
(*) means p < 0.05.

### 3.2. Aim 2: Effect of Covid-19 infection on in-hospital mortality

A total of 359 patients were identified that met the inclusion criteria. During the Pre-COVID-19 period, 197 patients were identified and none were excluded (54.9%). As previously stated, the Post-COVID-19 period identified 162 patients (45.1%) over the 5-month study period. During the Post-COVID-19 period, 54 patients (33.3%) had confirmed infections [Table 2]. In-hospital mortality during the Pre- and Post-COVID-19 periods were 16.24% and 25.3% (P = 0.034), respectively. Total in-hospital mortality amongst both groups was 20.33%. Patients with confirmed infections had an in-hospital mortality rate of 55%. COVID-19 infection had a strong association with mortality before discharge (OR, 5.45, P < 0.001) [Table 4].

### 4. Discussion

Traumatic brain injuries are recognized as a major cause of death and disability globally. Although regional differences in cause may exist, the incidence amongst the elderly is steadily

**Table 4**
Comparing two groups (COVID-19 positive and negative) in term of qualitative variables.

| Variable | | Covid19 Positive N (%) | Statistical test Negative N (%) | Statistical test |
|---|---|---|---|---|
| Gender | Male | 34 (37.7%) | 56(62.3%) | P = 0.240 |
| | Female | 20 (27.7%) | 52 (72.3%) | |
| Intracranial Surgery | Yes | 21(31.8%) | 45 (68.18%) | P = 0.865 |
| | No | 33 (34.3%) | 63 (65.7%) | |
| In-Hospital Mortality | Yes | 30 (73.1%) | 11 (26.8%) | ***P < 0.001** |
| | No | 24 (19.8%) | 97 (80.1%) | |
| Light Reflex | Both Pupils Reactive | 43(32.3%) | 90 (67.6%) | P = 0.865 |
| | One Pupil Fixed | 11(37.9%) | 18 (62.1%) | |
| Hyperglycemia | Yes | 27 (42.18%) | 37 (57.81%) | P = 0.062 |
| | No | 27 (27.5%) | 71 (72.4%) | |
| Hypotension | Yes | 26(57.7%) | 19 (42.2%) | ***P < 0.001** |
| | No | 28 (23.9%) | 89 (76.1%) | |
| Cardiovascular Disease | Yes | 27 (40.9%) | 39 (59.1%) | P = 0.453 |
| | No | 20 (15.2%) | 111(84.7%) | |
| Anticoagulant Drugs | Yes | 10 (37.1%) | 17 (62.9%) | P = 0.660 |
| | No | 44(35.5%) | 91 (67.5%) | |
| Rotterdam Score | 1 | 5 | 12 | P = 0.312 |
| | 2 | 24 | 51 | |
| | 3 | 16 | 29 | |
| | 4 | 4 | 10 | |
| | 5 | 5 | 4 | |
| | 6 | 0 | 2 | |
| Antiplatelet Drugs | Yes | 32(34.1) | 62 (65.9%) | P = 0.867 |
| | No | 22 (32.3%) | 46 (67.7%) | |
| Cause Of Trauma | Motor Vehicle Accident | 32 (39.5%) | 49(60.5%) | P = 0.743 |
| | Fall | 14 (25.9%) | 40 (74.1%) | |
| | Others | 8(29.6%) | 19(70.4%) | |

increasing and it remains a global priority. In this study, values that may aid in the prediction of patient outcomes and mortality rates are explored. Of note, this study sheds light on the influence of COVID-19 on the outcomes of elderly TBI patients.

### 4.1. Aim 1: Predictors of In-hospital mortality

The results of this study showed that the overall rate of in-hospital mortality amongst the elderly population during the COVID-19 pandemic due to moderate to severe TBI was 25.3% percent, an increase from the same period time in the prior year (16.24%). It is well established that elderly adults with TBI have higher mortality when compared to their younger counterparts [10–11]. Overall, advanced age and comorbid conditions are linked to slower functional gains in rehabilitation, post-traumatic neurological disorders, subsequent cognitive impairment, and poorer outcomes in older adults [12]. In a retrospective study conducted in the largest level 1 tertiary care facility in India, an in-hospital mortality rate of 34.56% was shown in adults with moderate and severe TBI [10]. However, in other studies, in-hospital mortality in elderly patients who suffer severe TBI's can range as high as 76% [13–14]. High levels of variability across studies may signify variation in design, regional treatment modality, demographic, or pre-injury function. A lower mortality rate than expected can represent the expertise of surgeons, early detection, and deliberate post-operative care.

Furthermore, patients with hyperglycemia had a two-fold increase in mortality (OR: 2.39) and those who were hypotensive had about four and half times increased mortality (OR: 4.57). In hyperglycemic TBI patients, lactic acidosis, inflammation, blood–brain barrier rupture, vessel hyper-permeability, and vessel disorders occur at higher rates and contribute to unfavorable outcomes in patients [15]. A history of concomitant use of anticoagulant medications was also associated with increased mortality with an OR of 2.41. TBI patients depend heavily on cardiac output and are more dramatically affected by cardiovascular compromise; it is postulated that those with higher troponin enzyme levels and compromised myocardial workload have higher incidences of death, although this finding cannot be supported by the results of this study [16–17]. The topic of anticoagulation in elderly TBI patients has been an object of controversy. Although the use of anticoagulation increases bleeding risk after a TBI, it has not to be linked to increased mortality in elderly TBI patients [18]. Fortuna et al concluded that there was no significant difference in mortality or length of hospital stay [19]. Nevertheless, the impact of anticoagulation in elderly patients with TBI will continue to be a discussion as more investigation on this topic is warranted [20,21].

Prediction of mortality among TBI patients has been widely reviewed. A machine-learning study conducted by Matsuo et al developed an algorithm that predicted in-hospital poor outcomes within 91%. The study concluded that age, Glasgow Coma Scale, fibrin/fibrinogen degradation products, and blood glucose were the most predictive factors of mortality amongst both TBI and elderly patients [22]. Abnormalities in these predictive criteria have been associated with inferior outcomes [23,24]. In this study, those who survived had significantly higher GCS scores (8.25 vs 5.63, P < 0.001). Patients with lower CGS scores tend to have poorer neurologic exams. While the strengths of GCS include its ease to measure and reliability, the use of GCS is limited in sedated patients, patients intoxicated with alcohol or drugs, and patients with facial fractures [24]. Both IMPACT and CRASH models demonstrate the prognostic value in predicting mortality within two weeks and unfavorable outcomes utilizing factors such as GCS, pupil response, age, hypoxia, glucose, and even hypotension [25]. However, these models are revealed to be less precise when used for the elderly population and fail to consider comorbid conditions such as cardiovascular disease. However accurate, the present prognostic model is limited in the realm of elderly patients. More support is needed to elucidate specific factors predictive of outcomes in this patient population.

### 4.2. Aim 2: Effect of COVID-19 on in-hospital mortality

Between March 2nd and August 1st of 2020, COVID-19 infected elderly patients with moderate to severe TBI were at significantly increased odds (OR, 5.47, P < 0.001) of expiring before discharge. There has been limited evidence that supports the neurologic manifestations of COVID-19 presenting as hemorrhagic and ischemic cerebral injury, headache, dizziness, and encephalopathy [26–27]. It is still unknown the extent of CNS involvement and how infection influences microcirculation and potentially diminishing oxygen delivery. There's even speculation that COVID-19 infection is linked to an increased risk of stroke. Although there is no direct causal relationship that links COVID--19, neurodegeneration, and morbidity, we experienced a statistically significant increase in the rate of in-hospital mortality when comparing the Pre-COVID period to the Post-COVID-19 period (16.24% compared to 25.3%, respectively) [28].

COVID-19 positive patients died at a higher rate than COVID-19 negative patients (55%). The overall COVID-19 mortality rates to date are approximately 2.3%, whereas, in patients aged 70 – 79, it is 10.9% and in patients ≥ 80 yo, it is 26.6% independent of TBI [29].

In our study, this was significantly larger and may be ascribed to regional differences. In a recent study conducted on risk factors for mortality in COVID-19, it demonstrated that mortality increases in age such that with each year additional year of life, the rate of death is increased by 0.079 [30]. This incremental increase in mortality has been attributed to underlying chronic disease and immunodeficiency, both of which are more prevalent in the elderly population [29]. A higher mortality rate among elderly TBI patients with COVID-19 is still speculative and in need of more exploration, although it is supported by the results shown in aim two. It has been reported that viral infections like COVID-19 could lead to systemic inflammation with a high level of different inflammatory parameters including C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), procalcitonin (PCT), interleukin-6 (IL-6), interleukin-10 (IL-10), interleukin-2R (IL-2R), serum amyloid A (SAA), and neutrophil-to-lymphocyte ratio (NLR) [31–34]. Several studies have demonstrated that the inflammatory parameters are closely associated with the COVID-19 severity and mortality [34–36]. In a recent systematic review and *meta*-analysis Mahat et al showed a significant increased serum concentrations of CRP, ESR, PCT, IL-6, IL-10, IL-2R, ferritin, SAA in severe COVID-19 patients in comparison with non-severe ones. Moreover, they reported significant increased levels of CRP, PCT, IL-6, ferritin, and NLR in non-survivors as compared to survivors. These inflammatory parameters could be used as predictors of the transition from mild to severe form of COVID-19 and could help the physicians to facilitate the early initiation of effective treatment [34].

It is supposed that the cumulative effects of TBI and coronavirus may have resulted in an increased rate of mortality. However, limitations in the care of hospitalized patients with COVID-19 in the context of a pandemic cannot be neglected. In this challenging time, nurses and healthcare workers were overwhelmed with the increasingly demanding workload caused by COVID-19. The patients and healthcare workers alike were left in physical and emotional distress, perplexity, and suffering as they mourned the death of patients, loved ones, and coworkers [37,38]. The increase in patient volume exacerbated an already present issue where, in Iran, inadequate personal protective equipment and deficiencies in the preparation of nurses and staff may have played a role

[39]. In a qualitative study by Karimi et al, the Iranian nurses were confronted with fear, anxiety, and major distress anticipating their death and the death of family members. Meanwhile, others dealt with staff shortage as well as lack of support and equipment [40,41]. In a qualitative study done on nurses' experiences during the outbreak, there was a perception of high-risk in working in the hospital environment because of the continual ambiguity of questioning who was infected, especially considering there is no definitive treatment for COVID-19 [40]. The compounded stress, lack of equipment, and perception of danger could have influenced the best possible care of TBI patients in the wards who were already at an increased need of deliberate consistent monitoring. Any care that is suboptimal in this setting increases the risk of mortality of these patients [42].

Our results showed that the COVID-positive TBI patients have a higher incidence of hypotension in comparison with COVID-negative ones. Koudelka et al reported the cases of five frail geriatric patients with sarcopenia and controlled hypertension who became hypotensive after COVID infection. They found that the previously well-established therapy was suddenly too intensive for those patients [43].

The cytokine storms that could be induced by COVID-19 may be a potential reason for the hypotension in COVID-positive patients [44]. The significant increase in plasma levels of certain interferons, interleukins, and chemokines could lead to capillary leak, resulting in pulmonary edema and hypotension.

This cytokine-induced hypotension could present even in milder cases of cytokine release syndrome and could result in the need for vasopressor support [44].

Limitations are present in the study. Our binary measure of outcomes limits our ability to gauge mortality such that expiring weeks to months after discharge can be mischaracterized as favorable. Furthermore, limitations on the nature of injuries requiring intracranial surgery and limitations in data and history collection can potentially skew outcomes. Future directions may include stricter inclusion criteria. With respect to COVID-19, a better method of comparing the change in outcomes caused by the pandemic is urged to decrease the global burden of the disease. This study conveyed a unique property of measuring a specific demographic at Taleghani Hospital pre and post COVID-19. The incidence and mortality rate at this institution may greatly differ from the global average. Moreover, the study design resulted in the minimization of demographic and regional changes throughout the year, thereby allowing changes due to the COVID-19 pandemic to be most adequately measured. More studies are needed to illuminate the effects of TBI in countries with low to medium income, especially where the incidence is higher than the overall global rate.

## 5. Conclusion

This study was aimed to evaluate predictors of in-hospital mortality among elderly patients with moderate to severe TBI throughout the COVID-19 pandemic as well as compare in-hospital mortality during the COVID-19 pandemic to the previous year. We found an increased incidence of in-hospital mortality in patients with hyperglycemia, hypotension, use of anticoagulant medication, and most significantly COVID-19 infection. The results also indicate a significant association of positive COVID-19 infection with advanced age and lower GCS score in this patient population. Elderly patients with moderate to severe TBI expired before discharge at higher rates during the COVID-19 pandemic. Furthermore, those who had coronavirus infection had 5.45 times increased in-hospital mortality. It is suggested that more attention is paid to the therapeutic care of the patients who have these risk factors with the intention of relieving the global burden of the pandemic.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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