Trauma Monthly 2025; 30(6): 1640-1648

10.30491/tm.2025.469561.1751

Trauma Monthly
Research Article

Modelling Prognostic Factors on Traumatic Care Pathways: An Application of Multistate Models

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Received 2025-01-08; **Accepted** 2025-10-25; **Online Published** 2025-12-29

Abstract

Introduction: Traumatic experiences are commonplace worldwide and have been proven to have detrimental effects on health. Unlike traditional survival analysis, which focuses on a single endpoint, multistate models are beneficial for evaluating the progression of multiple health conditions over time. The primary goal of this paper is to employ a multistate model to ascertain the patterns in hospitalizations among traumatic patients.

Method: In this longitudinal study, 502 eligible trauma patients who were referred to Shahid Rajaee Hospital in Shiraz, Iran, were chosen and followed from July 2018 to March 2019. A Semi-Markov Multistate model was utilized in the current study. Patients were assumed to transition between five states. Transition times (triage → general ward, triage → death, general ward → Intensive Care Unit [ICU], general ward → death, and surgical ward → death) were assumed to follow an exponential distribution. The hazard ratio (HR) for each covariate was estimated for each transition.

Result: Based on in-hospital triage evaluations, some patients needed surgery. Injury Severity Score (ISS) more than 15 (HR= 1.41), blunt trauma with brain injury (HR=2.15), hypotension (HR=1.41), and low pulse rate (HR=1.40) increased the probable requirements of the surgery. Following surgical treatments, patients with moderate Glasgow Coma Scale (GCS) were more likely to die (HR=1.42). Further, those who had experienced blunt trauma and brain damage had a lower chance of death following surgery (HR=0.62). The need for intensive care directly after triage is more likely in cases with a severely low GCS score.

Conclusion : This study confirmed that elderly patients are at lower risk of surgical interventions after ICU. Cases with more injuries were more likely to require surgery after triage. Identifying specific prognostic factors that significantly impact the progression and outcomes of traumatic care can help healthcare providers prioritize interventions and allocate resources more effectively, ultimately enhancing patient outcomes.

Keywords: traumatic care, pathways, model, prognostic factors.

Introduction

Trauma is a global health issue harming 10,000 people every day in both developed and developing nations. Exposure to traumatic events is widespread around the world and has a serious deleterious effect on health [1]. The effects of trauma vary based on the individual life circumstances, environment, and degree of resilience. Trauma can take many different forms. Traumatic events such as family and social violence, rapes and assaults, natural disasters, wars, accidents, and predatory violence subject people to such horror and threat that it may temporarily or permanently alter their capacity for coping, their perception of biological threat, as well as their concepts of themselves [2].

Healthcare administrators play a critical role in identifying and preventing patients' poor health outcomes. It is advised that fundamental information and comprehension of trauma be a part of healthcare education at all levels and disciplines, similar to other extremely contagious diseases [3, 4]. Death is regarded as the ultimate outcome in the majority of studies that have looked into the survival of trauma patients. In-hospital mortality and complications have been the main topics of studies on surgical result, but in reality, there are a few additional objects and factors that take place between the admittance and the death [5].

The in-hospital case fatality rates for initial hospitalization may not be a suitable method for ascertaining the efficacy of trauma treatment since there are substantial states from the admission to death as eventual event. Operating room, ward hospitalization, intensive care unit (ICU) admission, discharge, or, even death after discharge are intermediate events which individuals may experience along their traumatization [6]. Transfers between these states are strongly correlated with patient survival, and they may have multiple times of displacements between the surgical ward and the ICU.

Traditional survival techniques cannot be utilized to analyze these complex connections. Over time, events are characterized by multistate models (MSM) as changes between various states. The transition hazards are the statistical quantities in these techniques [7, 8]. Multistate models are a valuable statistical tool in assessing the outcomes of trauma patients as they allow for a detailed understanding of the progression through multiple health states over time.

These models have the ability to examine the influence of covariates on various states, the probabilities of transitioning from one state to another, and the trajectory of the disease's progression. These techniques can aid researchers in developing a better grasp of the progression of the process of disease [9]. Multistate models in trauma are employed to analyze the transition of patients from one health state to another after a traumatic injury. These models can support understanding the long-term effects of trauma on patients as well as identify factors that may influence their recovery. When accurate data and statistics on the prevalence of trauma mechanisms along with their effects are accessible, the majority of preventive techniques are successful in the event of trauma. Thus, it is essential to apply robust statistical methods for data analysis as this will have a significant influence on the choices made by health policymakers.

Recently, MSM have been used extensively in clinical studies with a terminal event [10]. Traditional statistical methods consider single outcomes while failing to describe the transitions and multiple health states. Multistate models enable the analysis of different prognostic factors that affect the progression of patients' care, which is helpful in providing valuable insights about treatment. Although multistate techniques have been developed in various settings, but they have rarely been applied in trauma research. Thus, the primary goal of this paper is to use a multistate model to ascertain the patterns in hospitalizations among traumatic patients.

Methods

Study population

In this prospective cohort study, all trauma patients who were referred to the Cardio Pulmonary Resuscitation room of the Shahid Rajaee Trauma Center in Shiraz, Iran, from July 2018 to March 2019, were recruited and followed until they passed away or were discharged from the hospital.

Data Collection

Demographic data about patients, the timing of each transfer between different hospital units, factors related to disease progression that influenced these transfers, and factors affecting the number of days spent in various units are all extracted and reviewed from hospital records. Finally, 502 patients were eligible for inclusion in this study. The inclusion criterion was age> 16 years. Patients with incomplete records and those transferred to another hospital were excluded from the study.

Modeling Approach

The structure of multistate models is not unique. The complexity of these models heavily depends on the number of states and their possible transitions. We chose to use the Markov multistate model for the following reasons: initially, the complexity of care pathways, which is a critical point for traumatic injuries. A semi-Markov multistate model is an appropriate method to estimate probabilistic nature of movement between different states over time. The second reason concerns time-dependent covariates, for which the likelihood of transitioning from one state to another can vary over time; the effect of these covariates is well described at each transition by Markov models. A Semi-Markov Multistate model has been used in the current study. According to the model's assumption, individuals' rates of progression to the subsequent state are independent of their rates of progression into the preceding state. It is also crucial to consider the sequence of transfers and the length of stays in each hospital section. Patients may move between the surgical unit and the ICU only a limited number of times, and this movement directly affects their survival. The model includes all clinically plausible transitions observed in our dataset. Transitions included: triage→death, triage→ICU, triage→surgical ward, general ward→ICU, general ward→death, surgical ward→death, ICU→ surgical ward, and vice versa. The multistate model and its transitions are displayed in Figure 1. In Semi-Markov Multistate models, owing to the complex form of the waiting-time distribution and the variables employed in the model, the number of parameters is significant relative to the size of the data set, which may prevent the model from converging.

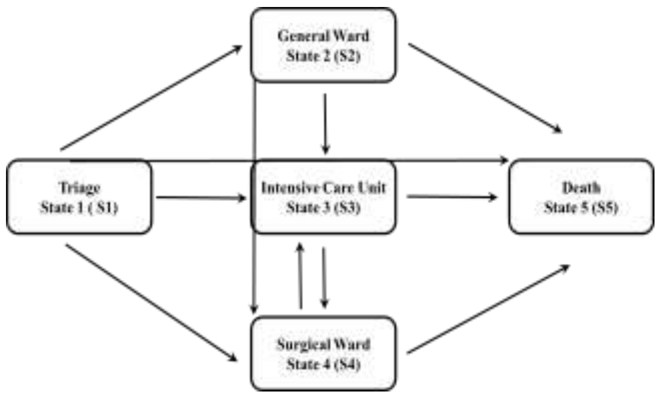

Figure 1: Multi-state model for traumatic care pathways

Statistical details

Since we had a small number of data points and a large number of variables in our model, evaluating all variables led to non-convergence. Hence, we evaluated our model with each variable separately, using a Semi-Markov Multistate univariate model with the default Weibull distribution for the waiting time. This univariate analysis also provides the shape parameter (nu) of the default Weibull distribution, allowing us to select a more suitable distribution for the waiting time. According to univariate analysis, four transitions (Triage → death, general ward → ICU, general ward → death, ICU → surgical ward) followed an exponential distribution, whereas the remaining transitions followed a Weibull distribution. The choice of the exponential distribution for specific transitions in the Semi-Markov Multistate model was based on the findings of the univariate analysis. In this analysis, the shape parameter (nu) of the default Weibull distribution was estimated for each variable and each transition. When the estimated shape parameter was approximately 1, the exponential distribution was selected, as the Weibull distribution reduces to the exponential distribution in such cases. This is justified by the memoryless property of the exponential distribution, which assumes a constant hazard rate. Significant variables from the univariate analysis ($p < 0.20$) were included in the final model. After confirming the variables and the appropriate waiting-time distribution matrix, the Semi-Markov Multistate model was run with all significant variables. In our semi-Markov multistate model, covariates were modeled as baseline values measured at hospital admission. The following variables were statistically significant in univariate analysis included in the final model: Injury Severity Score (ISS), Age, Glasgow Coma Score (3-8 severe, 9-12 moderate, >12 mild), oxygen saturation (O2sat), White Blood Cell (WBC), systolic blood pressure (SBP), diastolic blood pressure (DBP), base excess (BE), pulse rate (PR), and blood pH (PH). Given the variety of patients being admitted to the trauma ICU, they were classified into three categories: blunt trauma with brain injury, blunt trauma without brain injury, and penetrating trauma with and without brain injury. Some continuous variables were categorized to facilitate clinical interpretation, in line with established trauma care protocol. Patients who improved and were discharged before the end of the study period have been considered censored.

In the current analysis, the mechanism for missing data was missing-at-random (MAR). According to the literature review, multiple imputation was found to reduce bias and increase precision compared with other methods [11]. Variables with less than 5% missing data were imputed, leading to the creation of ten imputed datasets. Convergence was evaluated using density plots comparing the distributions of observed and imputed data for each variable (Figure S1). The missing data were replaced using Multiple Imputation (MI) methods in the MICE package in R, with the "SemiMarkov" package employed for Semi-Markov Multistate analysis [12]. All statistical analyses were undertaken using R software version 3.6.2.

Results

In this study, 502 patients were included. The mean age was estimated at 39.8±19.2 years, with 14% of participants aged 65 years or older. The median follow-up time was 51.9 months. The men outnumbered women in this population (87% vs. 13%). Of all patients, 87% experienced blunt trauma with brain injury. More than half of patients (56%) had ISS more than 15. Most of them had mild GCS (55%). O2 saturation was lower than 90% in 76% of cases. More details about clinical factors and demographic data are reported in Table 1. The number of patients in each transitions are provided in Table 2.

The results for the semi-Markov model on statistically significant variables in the multivariate models are outlined in Table 3. In the following, interpretations are given separately for each transition.

Triage → General ward

Individuals with moderate GCS are less likely to be admitted to the general ward after triage than those with mild GCS (HR=0.12). This is while cases with O2 saturation less than 90% (HR=2.69) and abnormal BE (HR=3.16) are more likely to be hospitalized in the general ward.

Triage → ICU

Intensive care requirements after triage are directly assessed; they are more likely in cases with a severe GCS score. Also, patients who suffer from diminishing O2 saturation and abnormal PH are at risk of ICU admission.

Triage → Surgery ward

Based on in-hospital triage evaluations, some patients needed surgery. As presented in Table 3, ISS more than 15 (HR= 1.41), blunt trauma with brain injury (HR=2.15), hypotension (HR=1.41), and low pulse rate (HR=1.40) would elevate the probability of surgery requirement.

Triage → Death

The hazard ratio for patients with ISS >15 was lower than for patients with ISS <15 in this transition. This means patients with more injuries are less likely to die (HR=0.26). Another variable for this transition, which was statistically significant, was low systolic blood pressure, an effective factor in lowering the probability of death after triage (HR=0.26).

General ward → Death

In comparison to cases of penetrating trauma with/without brain injury, patients who had suffered blunt trauma with brain injury were less likely to die in the general ward. (HR=0.36)

ICU ↔ Surgery ward

ISS greater than 15 (HR=0.63), severe GCS (HR=0.52), and elderly patients (Age >65 years) are less likely to undergo surgery following ICU admission. While the risk of post-operative problems requiring intensive care for patients with severe GCS was calculated at 1.91, it was clinically and statistically significant.

Surgery ward → Death

Following surgical treatments, patients with moderate GCS are more likely to expire (HR=1.42). Meanwhile, those who had experienced blunt trauma and brain damage have a lower chance of death following surgery (HR=0.62).

The number of days required to stabilize each patient's condition is presented in the figures in the supplementary file. As depicted in Figure S.1, the chance of discharge is extremely high along the initial stages of moving from triage to surgery and gradually diminishes over time. When a patient requires surgical treatment after admission to the ICU, the discharge rate is relatively constant over time (Figure S.2). In the supplementary file, additional figures are provided for different transitions. The number marked in Figure S.3 indicates that it takes about 0.13 days to stabilize the condition of trauma patients after transferring from triage to ICU. After this period, the risk of death of these patients is significantly reduced.

Table 1. Descriptive Information of Trauma Patients in Shahid Rajaee Hospital.

Independent variable		Count	Percentage
Gender	female	66	13
	male	436	87
Age	<65	433	86
	≥65	69	14
ISS	≤15	220	44
	> 15	282	56
GCS	3-8 (severe)	139	28
	9-12 (average)	86	17
	13-15 (mild)	277	55
O2sat	<90	381	76
	≥90	121	24
SBP (mmHg)	<90	41	8
	≥90	461	92
DBP (mmHg)	<60	62	12
	≥60	440	88
RR	≤20	342	68
	>20	160	32
PR	≤100	275	55
	>100	227	45
BUN(mg/dl)	≤20	417	83
	>20	85	17
WBC (mm^3)	<11	173	34
	≥11	329	66
PH	7.35-7.45	256	51
	<7.35 , >7.45	246	49
BE	< -8	110	22
	≥ -8	392	78
Trauma Mechanism (TM)	Blunt Trauma with brain injury	435	87
	Blunt Trauma without brain injury	20	4
	Penetrating Trauma with or without brain injury	47	9
Discharge	Recovery	412	82
	Death	90	18
total		502	100

Table 2: The number of patients in each transitions

Status	**Status**					
	Triage	General ward	ICU	Surgical ward	Discharge	Death
Triage	0	98	252	140	12	11
General ward	0	0	12	68	19	0
ICU	0	0	0	331	74	74
Surgical ward	0	0	141	0	399	5

Table 3: Statistically significant Prognostic factors for each transition with hazard ratios and their 95% confidence interval in Semi-Markov Multistate Model

Variable	Transition	Hazard rate	SE	P-Value
ISS (≥ 15)	$1 \rightarrow 4$ $1 \rightarrow 5$ $3 \rightarrow 4$ $4 \rightarrow 5$	1.412 (1.13 – 1.75) 0.260 (0.08 – 0.77) 0.635 (0.50 – 0.80) 0.628 (0.50 – 0.77)	0.11 0.55 0.12 0.11	0.002 0.015 0.0002 < 0.001
Age (≥ 65)	$3 \rightarrow 4$	0.583 (0.40 – 0.86)	0.19	0.004
GCS(moderate)	$1 \rightarrow 2$ $1 \rightarrow 3$ $4 \rightarrow 5$	0.127 (0.05 – 0.28) 2.052 (1.44 -2.91) 1.429 (1.09 – 1.87)	0.42 0.18 0.14	< 0.001 < 0.001 0.010
GCS(Sever)	$1 \rightarrow 3$ $3 \rightarrow 4$ $4 \rightarrow 3$	2.085 (1.50 – 2.88) 0.527 (0.40 – 0.69) 1.917 (0.23 – 2.97)	0.16 0.14 0.22	< 0.001 < 0.001 0.004
Trauma Mechanism (TM) (Blunt Trauma with brain injury)	$1 \rightarrow 4$ $2 \rightarrow 5$ $4 \rightarrow 5$	2.151 (0.34 – 3.42) 0.364 (0.12 – 1.03) 0.628 (0.41 – 0.94)	0.24 0.53 0.21	0.001 0.050 0.025
O2sat (< 90)	$1 \rightarrow 2$ $1 \rightarrow 3$	2.691 (1.05 – 6.88) 1.406 (1.03- 1.91)	0.48 0.16	0.039 0.033
BPsys (< 90)	$1 \rightarrow 4$ $1 \rightarrow 5$	1.411 (1.13 – 1.75) 0.260 (0.08 – 0.77)	0.11 0.55	0.002 0.015
BE (Base deficit ≥ -8)	$1 \rightarrow 2$	3.161 (0.92 – 10.80)	0.63	0.068
PR (> 100)	$1 \rightarrow 3$ $1 \rightarrow 4$	0.520 (0.39 – 0.69) 1.406 (0.990 – 0.993)	0.15 0.18	< 0.001 0.057
PH (< 7.35 , > 7.45)	$1 \rightarrow 3$	1.544 (1.61 – 2.05)	0.15	0.003
Reference level: ISS < 15, age: < 65, GCS: Mild, O2sat: > 90, BPsys > 90, BE < -8, PR<100, PH: 7.35 -7.45				

Discussion

One of the most important issues for global health is trauma, which causes more than 5 million deaths annually. Identifying the prognostic factors would be helpful in the management of trauma victims [13]. In addition to prognostic factors, intermediate events can also affect survival. Multistate models can be applied to use all information from different states and events [14]. The primary goal of this study was to ascertain the survival process for trauma patients while considering all states and factors impacting the course of the disease. According to the current results, this study confirmed that elderly patients are at a lower risk of surgical interventions post-ICU. Current analysis results indicated that only 14% (approximately 70 cases) involved patients aged 65 years or older. The possibility of surgery is related to the mechanism and severity of trauma. Falls are the leading cause of trauma in this age group, which may not be severe enough to mandate a surgical intervention. Viewing from another aspect, due to their frailty, those with severe injuries may experience pre-hospital mortality. However, if needed, indications for surgical intervention are not limited solely by age. In addition, this finding may be associated with increased morbidity or mortality. This reason is a poor prognostic factor for the outcome in this age group. It would also be related to their susceptibility and frailty for post-operative complications. Indeed, the procedure is riskier for this patient group if they have additional comorbidities. Moreover, older adults generally benefit from conservative care owing to their diminished physiological reserve, which limits their capacity to recuperate after significant surgical procedures. Indeed, better care can result in less morbidity and mortality, while multiple system injury is a marker of severe injury and an increased chance of complications and death. This finding needs further scrutiny, and the presented causes are not satisfactory. Since this group of patients has multiple chronic illnesses, surgery is not common in the elderly traumatic patients compared to the younger population. This was in line with Jimmy's *et al* study too[15]. Similar to other studies, we observed that cases with more injuries (ISS > 15) would require surgical intervention after triage, as reported in [16, 17]. This may be justified based on triage protocols where surgical operations are prioritized for patients with high ISS to prevent further complications such as hemorrhage, infection, or organ failure. Further, we found that patients with an ISS greater than 15 are less likely to die after triage. These findings, which appear counterintuitive given the typical association of higher ISS with increased mortality, may be affected by survival bias. Specifically, the study only included patients who survived to triage and were admitted to Shahid Rajaee Hospital, excluding those who died pre-hospital or prior to triage. Patients with high ISS who reach triage may represent a subgroup with less severe outcomes, as those with the most critical injuries may not survive to be included in the analysis. This survival bias may contribute to the observed lower hazard of death for high-ISS patients. In this regard, Ann *et al*. reported that triage protocol efficiency reduces mortality risk. She found that a proper level of treatment would reduce adverse clinical outcomes resulting from protocol application in triage [18]. Another study also reported that the ISS mean was higher among non-surviving trauma patients[19].

As shown in the Results section, GCS was identified as a predictor of ICU requirement after triage. The statistical analysis's conclusion that GCS predicts ICU admission highlights the clinical component of the problem. Patients are given priority for intensive care when this score is employed in triage protocols. It provides medical professionals with a quick, easy, and trustworthy way to determine whether patients require specialized treatment immediately after trauma. Similar results have been observed in other studies [20, 21]. The current study found that abnormal PH predicts ICU admission after triage, as observed in other studies. The potential importance of this point has been noted in other clinical studies. Severe metabolic acidosis (base deficit ≥ -8) is known as a risk factor for mortality, so intensive care is essential for this group of patients [22]. Abnormal pH levels, including acidosis (low pH) or alkalosis (high pH), are important indicators, as they signal severe underlying conditions such as respiratory failure, renal dysfunction, or shock that require intensive care. In triage settings, where decisions must be made quickly to prioritize ICU admissions, pH levels are a vital parameter for clinicians. This would help them assess the patient's overall physiological stability and identify those at risk of deterioration. In urgent triage situations, a simple biomarker would facilitate decision-making. As observed in other studies, this biomarker underscores the importance of pH in clinical practice, suggesting that abnormal pH should be carefully considered in trauma and critical care triage protocols to improve survival rates.

The present study found that hypotension (systolic blood pressure lower than 90) was associated with surgery requirement, and death was less likely after triage. The need for surgery in hypotensive patients is part of life-saving measures aimed at reversing shock and preventing further deterioration. Mazen *et al* demonstrated that traumatic cases with hypotension in the emergency department or in a pre-hospital management frequently required ICU and experienced a prolonged duration of hospital stay [23]. In recent years, various studies have focused on the therapeutic effect of hydrogen in traumatic patients. Thus, this study evaluated its effect on intermediate events and found that PH plays a critical role in ICU requirements after triage. It would increase the hazard of ICU admission by 1.54 times. As a possible explanation, one can mention hydrogen's role in protecting against cellular damage. In trauma patients, oxidative stress post-trauma (due to blood loss or shock) leads to cellular damage and worsened outcomes. Since hydrogen may neutralize reactive oxygen species (ROS) and lower inflammation, it has the potential to be used as a therapeutic agent. This might enhance recovery and mitigate consequences such as organ failure [24, 25].

Regarding the statistical method, the MSM has been employed in numerous research studies, particularly those on chronic illnesses such as cancer, as it provided some new insights into how patients' illnesses were progressing [26, 27]. The important point about this method is the reduction in the standard errors of estimation. Also, the influence of prognostic factors on intermediate events along the course of the disease has been highlighted by multistate models [7].

One of the strengths of this study was that it was the first applied study for using MSM on trauma data. As such, reducing bias in estimation is one of this method's achievements. Also, this study identified specific prognostic factors that significantly impact the progression and outcomes of traumatic care. These insights can help healthcare providers prioritize interventions and allocate resources more effectively, ultimately improving patient outcomes. The study's limitation was the limited data and the large number of variables in our model, so evaluating all the variables would cause non-convergence. Further, we acknowledge the possibility of survival bias, as only patients surviving to triage were included.

Conclusion

According to our findings, the Semi-Markov Multistate model with 11 possible transitions between five states—Triage, Emergency, Intensive care unit, Surgery, and discharge—plus 14 potential variables affecting trauma patients was the best, most efficient mechanism for our trauma data. The usage of these findings in the context of trauma care may enhance the early detection of patients in need of critical care and direct the establishment of innovative hydrogen therapy treatment approaches. Clinical trials and long-term studies should be the primary focus of future research to validate the effectiveness of hydrogen treatment and the contribution of pH management to improved trauma care outcomes. Trauma teams may be able to improve patient care, reduce intensive care unit hospitalizations, and eventually boost the survival and recovery rates of trauma patients by incorporating these findings into clinical practice.

Acknowledgments

The valuable contribution of Trauma Research Center, Rajaee (Emtiaz) Trauma Hospital, Shiraz University of Medical Sciences is greatly appreciated. This study was extracted from an MSc thesis in Biostatistics by Parisa Safarinejadian (18660).

Conflict of Interest Disclosures

There are no conflicting interests listed by the authors.

Funding Sources

No Funding.

Authors' Contributions

Z. Sh. supervised and designed the study. F. J. and P. S. collected the data, performed the data analysis, and drafted the initial manuscript. Sh. P. and L. Sh. served as clinical consultants.

Ethical Statement

The review board of Shiraz University of Medical Sciences reviewed this study as a minimal-risk investigation using information gathered for standard clinical practice. It waived the need for informed consent (IR.SUMS.REC.1398.302).

Declaration of Generative AI and AI-assisted technologies

No AI-assistance was used.

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