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Prediction of postinjury multiple-organ failure in the emergency department: Development of the Denver Emergency Department Trauma Organ Failure Score

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Abstract

Background—Multiple-organ failure (MOF) is common among the most seriously injured trauma patients. The ability to easily and accurately identify trauma patients in the emergency department at risk for MOF would be valuable. The aim of this study was to derive and internally validate an instrument to predict the development of MOF in adult trauma patients using clinical and laboratory data available in the emergency department.

Methods—We enrolled consecutive adult trauma patients from 2005 to 2008 from the Denver Health Trauma Registry, a prospectively collected database from an urban Level 1 trauma center. Multivariable logistic regression was used to develop a clinical prediction instrument. The outcome was the development of MOF within 7 days of admission as defined by the Sequential Organ Failure Assessment (SOFA) score. A risk score was created from the final regression model by rounding the regression β coefficients to the nearest integer. Calibration and discrimination were assessed using 10-fold cross-validation.

Results—A total of 4,355 patients were included in this study. The median age was 37 years (interquartile range [IQR], 26–51 years), and 72% were male. The median Injury Severity Score (ISS) was 9 (IQR, 4–16), and 78% of the patients had blunt injury mechanisms. MOF occurred in 216 patients (5%; 95% confidence interval, 4–6%). The final risk score included patient age,

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Authorship: J.A.V. and J.S.H. had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. J.A.V., R.L.B., and J.S.H. provided the study concept and design. J.A.V., N.S., C.G., and J.S.H. performed the acquisition of data. J.A.V., M.M.L., E.H., N.S., R.L.B., C.G., E.E.M., and J.S.H. performed the analysis and interpretation of data. J.A.V. and J.S.H. drafted the manuscript. J.A.V., M.M.L., E.H., N.S., R.L.B., C.G., E.E.M., and J.S.H. provided critical revision of the manuscript for important intellectual content. J.A.V., M.M.L., E.H., and J.S.H. performed the statistical analysis. J.A.V. and J.S.H. obtained funding. J.A.V., E.H., and J.S.H. provided administrative, technical, or material support. J.A.V. and J.S.H. provided study supervision.

intubation, systolic blood pressure, hematocrit, blood urea nitrogen, and white blood cell count and ranged from 0 to 9. The prevalence of MOF increased in an approximate exponential fashion as the score increased. The model demonstrated excellent calibration and discrimination (calibration slope, 1.0; *c* statistic, 0.92).

Conclusion—We derived a simple, internally valid instrument to predict MOF in adults following trauma. The use of this score may allow early identification of patients at risk for MOF and result in more aggressive targeted resuscitation and improved resource allocation.

Keywords

Trauma; organ failure; emergency department; resuscitation; clinical prediction instrument

Trauma is the leading cause of death in the United States in individuals age 1 year to 44 years.^{1–3} Trauma has significant economic and societal impact, with costs of unintentional injuries alone accounting for \$406 billion annually, lost work-place productivity estimated at \$80 billion, and lifetime medical care estimated at \$326 billion.⁴

Multiple-organ failure (MOF) is common among the most seriously injured trauma patients; organ failure in one or more systems has been found in 29% of all trauma patients.⁵ MOF is the leading cause of morbidity and delayed mortality among those who survive the immediate period after injury. Mortality of trauma patients with failure in three organ systems is approximately 67%, and mortality approaches 100% in individuals with failure of four organ systems.⁶ Because the morbidity, mortality, and associated health care costs^{7–9} following the development of MOF are high, early recognition and prevention of this syndrome rather than delayed treatment are important.¹⁰

Several scoring systems exist to grade the severity of traumatic injuries and to stratify trauma patients into mortality risk groups.¹¹ However, limited data are available for the prediction of MOF following trauma using data early in the phase after injury. Previous models to predict MOF in trauma have focused on variables obtained later (24–48 hours) in the hospitalization. Cryer et al.¹² analyzed these predictive models and found MOF already present in a high proportion of patients when current models were trying to predict whether it would occur. As such, they recommended that scoring for MOF begin on the day of injury. Currently, no such prediction instrument exists to identify trauma patients at risk for MOF early in their hospital courses.

The development of an instrument to accurately predict MOF after injury using variables from the prehospital and emergency department (ED) settings would facilitate timely identification of patients at risk for MOF, thereby potentially allowing for targeted, aggressive resuscitation to decrease the incidence of MOF. The objective of this study was to derive and internally validate a clinical prediction instrument that uses information available within 4 hours of injury to identify trauma patients who will develop MOF within 7 days of hospitalization.

Patients and Methods

Study Design and Setting

This was a retrospective cohort study from Denver Health Medical Center in Denver, Colorado. Denver Health Medical Center is a 477-bed urban safety net hospital and the Rocky Mountain Regional Level 1 Trauma Center, the only academic Level 1 trauma center in Colorado.¹³ The ED is the primary receiving facility for all trauma patients and has an approximate annual adult census of 60,000 visits, of which approximately 2,000 are included in the trauma registry and approximately 500 of which are classified as major trauma (defined by an Injury Severity Score [ISS] >15).

The study was approved by the Colorado Multiple Institutional Review Board.

Study Population

Consecutive trauma patients (≥ 18 years old) who presented to Denver Health Medical Center from January 1, 2005, through December 31, 2008, and who were entered in the trauma registry were included in this study. The trauma registry contains trauma patients who are admitted to the ED observation unit for at least 12 hours, admitted to the hospital, die in the ED, or are transferred from outside hospitals for further trauma care. Patients were excluded from this study if they (1) were younger than 18 years; (2) died in the ED; or (3) were transferred from another hospital.

Data Collection

Patients included in the trauma registry are identified from the ED log by a team of personnel specifically trained in the oversight of the trauma registry and in the acquisition of data. Data are systematically abstracted from the patients' medical records and entered into an electronic database (TraumaBase, Clinical Data Management, Conifer, CO). To maintain quality assurance, an internal review of approximately 20% of the trauma registry records is conducted on a regular basis using a standardized protocol. Each review is completed by registry staff members who did not perform the initial chart abstraction. Any data discrepancies identified in this review are presented to the trauma registry committee, and corrections are made through a consensus process.

Data obtained from the trauma registry for the study included demographics (age, race, ethnicity, and sex); prehospital care characteristics (paramedic response time, scene time, transport time); date and time of presentation to the ED; prehospital and ED vital signs within 4 hours of arrival (heart rate, respiratory rate, and systolic blood pressure [SBP]); prehospital and ED Glasgow Coma Scale (GCS) score within 4 hours of arrival; prehospital and ED intubation or cricothyroidotomy; the Abbreviated Injury Scale (AIS) for each body region (head, face, neck, chest, abdomen/pelvis, extremities, skin); ISS; DRG International Classification of Diseases—9th Rev. external cause of injury code; transfusions (the number and timing of packed red blood cells and fresh frozen plasma transfusions); hospitalization characteristics (whether the patient was admitted, admitted to the intensive care unit [ICU] and, if so, the number of ICU days; and survival to hospital discharge); and final diagnoses (DRG International Classification of Diseases—9th Rev. codes). Laboratory data obtained

within 4 hours of arrival were obtained from the hospital's computerized laboratory system (MiSYS Healthcare Systems, Raleigh, NC) and linked to patient data obtained from the trauma registry.

Outcome Measures

The primary outcome, development of MOF within 7 days of hospitalization, was assessed using the Sequential Organ Failure Assessment (SOFA) Score.¹⁴ The SOFA score is a valid measure of MOF and has been used to reliably assess the occurrence of MOF in trauma patients.¹⁵ This score characterizes organ dysfunction over time and has been demonstrated to predict mortality.^{15,16} The SOFA score consists of measures of function across six organ systems. The lowest values of the Pao₂/FIO₂ ratio, platelet count, GCS score, mean arterial pressure, and urine output and the highest values of total bilirubin, adrenergic agent use, and creatinine were recorded for each 24-hour period and used in the score calculation. The occurrence of multiple-organ dysfunction (MOD) was defined as a SOFA score of 1 or greater in two or more systems, and MOF was defined as a SOFA score of 3 or more in two or more organ systems on any of the first seven hospital days.¹⁴ Secondary outcomes collected for this study included ICU admission, ICU length of stay (LOS), hospital LOS, and in-hospital mortality. The SOFA score was used instead of the Denver Multiple Organ Failure Score to determine the primary outcome since the SOFA score includes measures of the nervous and coagulation systems to provide a granular evaluation of the development of MOF. In addition, the SOFA score includes platelets, and there has been a demonstrated association between thrombocytopenia after injury and progression to MOF in trauma patients.^{17–20}

The medical records of study patients admitted to the ICU at anytime during the 7 days following admission were reviewed by trained, blinded physician abstractors to obtain the measures in the SOFA score. The data to evaluate for MOF were assessed on admission and in 24-hour intervals for the first 7 days following hospitalization and were recorded in an electronic closed-response data collection instrument (Microsoft Access, Microsoft Corporation, Redmond, WA). The abstractors were trained to use the data collection instrument to systematically abstract each end point using standardized medical record abstraction methodology.²¹ Ten percent of the charts were reabstracted to verify reliability of the abstraction process. Interrater reliability was assessed to determine the overall agreement, and the median κ was 0.92 (interquartile range [IQR], 0.81–0.98).

Data Management and Statistical Analyses

Data were transferred electronically from the trauma registry and MiSYS into separate electronic spreadsheets (Microsoft Excel, Microsoft Corporation). Outcome data were manually entered into an electronic database (Microsoft Access, Microsoft Corporation). Each electronic file was then transferred into native SAS format using translational software (dfPower DBMS copy, DataFlux Corporation, Cary, NC). All analyses were performed using SAS version 9.2 (SAS Institute, Inc., Cary, NC).

Continuous data are reported as medians with IQRs, and categorical data are reported as percentages with 95% confidence intervals (CIs). The

For median values, 95% CIs were estimated with a percentile method using 2500 bootstrap replications.²²

The derivation of the instrument to predict the development of MOF proceeded in a systematic fashion using multivariable logistic regression. Fractional polynomials were used to assess the nonlinear relationship of continuous predictors,²³ and multiple imputation was used to provide unbiased estimates of regression coefficients in instances where data were missing.^{23–25} Ten replications of multiple imputation was performed with SAS-callable IVEware (Survey Methodology Program, Survey Research Center, Institute for Social Research, University of Michigan, Ann Arbor, MI). Multiple imputation has been shown to be a valid and effective way of handling missing data and minimizes the bias that may result from excluding such patients from the analyses and has been shown to be a valid strategy when the proportion of the missing data are large.^{23–27}

Bivariate statistical testing or automated variable selection techniques were not used to drive selection of variables in the model. Instead, candidate predictor variables were included in the model in a sequential manual fashion. Individual variable contributions to the model were then assessed by their influence on the regression coefficients of other included variables as well as the fit of the overall model as calculated by the Hosmer-Lemeshow goodness-of-fit statistic.^{26,27}

The first step consisted of including only patient demographics in the model. Because age was a continuous variable and its relationship with MOF was thought to be nonlinear, we used fractional polynomials to model its relationship with the outcome. This approach is considered superior to modeling continuous data as linear variables or arbitrarily identifying specific cutoff points within the variable.^{28,29} Using these results, we graphed the relationship between age and MOF to identify one or more logical inflection points by which the probability of MOF changed across the age range. This same approach was used to determine cutoff points for all continuous variables included in the final Denver ED Trauma Organ Failure (TOF) score, namely, hematocrit, SBP, blood urea nitrogen, and white blood cell count.

Subsequent steps included the addition of variables related to prehospital care characteristics, prehospital and ED vital signs and GCS score, prehospital and ED intubation or cricothyroidotomy, AIS, ISS, ED interventions, and laboratory data obtained within 4 hours of ED arrival. When considering the ED vital signs, GCS score, and laboratory data for inclusion in the score, only the most extreme values were evaluated for inclusion. A total of 37 variables were considered for inclusion in the model. A full model was developed to include all statistically significant variables defined by a $p < 0.05$.

Once the full model was developed, we retained age and individually removed other variables, beginning with those with the weakest association with the development of MOF. Cross-validation was performed after the removal of each variable, and new Hosmer-Lemeshow goodness-of-fit statistic and area under the receiver operating characteristic (ROC) curves were generated and compared with those of the preceding model. This pruning approach continued until no other variable could be removed without losing the

model's fit or discrimination. The final risk score was then created by rounding the variables in the final model to the nearest whole integer.

Internal validation of the final model was performed using 10-fold cross-validation. We plotted observed versus predicted MOF prevalence, used linear regression to fit a line through the plot, and estimated its slope to assess overall model calibration. We plotted a ROC curve and calculated the area under the curve to estimate discrimination.^{27,30}

Sample Size Estimation

The sample size for the study was estimated to minimize the possibility of overfitting the logistic regression model while maintaining the ability to include a relatively large number of predictors in the analysis. As a general rule, multivariable logistic regression analyses require a minimum event to predictor ratio of 10:1.²³ We estimated that the final model would include a maximum of 15 predictors and therefore estimated requiring 150 patients with MOF. Given an estimated ICU admission prevalence of 35% and a prevalence of MOF of 18% among those admitted to the ICU, we estimated requiring a minimum of 2,400 patients to complete this study.

Results

During the 4-year study period, 4,355 consecutive trauma patients met criteria for inclusion and therefore represent our study sample. The median age was 37 years (IQR, 26–51 years); 72% were male, 78% experienced a blunt injury mechanism, and the median ISS was 9 (IQR, 4–16). A complete description of the demographics and characteristics of the study sample is presented in Table 1.

Of the 4,355 patients, 1,670 (38%) were admitted to the ICU, with a median ICU LOS of 2.5 days (IQR, 1–8 days). The median hospital LOS was 4 days (IQR, 2–7 days). Among the 4,355 participants, 1,161 (27%) developed MOD, and of those with MOD, 97 (8%) died. In addition, 216 subjects (5%) developed MOF, and of those who developed MOF, 69 (32%) died. A complete description of the outcomes for the study sample is presented in Table 2.

Although all potential predictor variables obtained within 4 hours of arrival were evaluated for inclusion in the predictive model, the resultant clinical prediction instrument only included age, emergent intubation (defined as occurring in the prehospital setting or the ED), hematocrit, ED SBP, blood urea nitrogen, and white blood cell count. The remaining prehospital and ED characteristics, including other vital signs and GCS score, AIS (as measures of injuries to specific body regions), ISS, interventions, and other laboratory data within 4 hours of arrival, did not contribute to the final model. The resultant risk score ranged from 0 to 9 (Table 3).

Application of the risk score on the study sample demonstrated an approximately exponential increase in the prevalence of MOF with increasing risk score values (Fig. 1). With the use of a 10-fold cross-validation, the calibration curve for the model demonstrated a slope of 1.03 (Fig. 2), and the area under the ROC curve was calculated to be 0.92 (Fig. 3).

Discussion

The goal of our study was to develop an easy-to-use instrument that would accurately predict the development of MOF after trauma when applied in the ED. We derived the Denver ED TOF score, a clinical decision rule that accurately predicts MOF with data readily available in the clinical setting immediately following injury. Previously, no score existed to help identify trauma patients at risk for developing MOF early in the hospital course.

While several scoring systems exist to grade the severity of traumatic injuries and to stratify trauma patients into mortality risk groups,¹¹ limited data are available for the early prediction of MOF following trauma. Previously identified risk factors for MOF include older than 55 years, transfusion of more than 6 U of packed red blood cells in the first 12 hours, ISS of 25 or greater, base deficit of less than 8 mEq/L in the first 12 hours, and lactate greater than 2.5 mmol/L from 13 hours to 24 hours.^{12,31} No previous research, however, has systematically combined these or other potentially important predictors from the first several hours after injury into a multivariable risk model for the prediction of MOF.¹² This study represents the first attempt to derive and internally validate a score for trauma patients that uses data from the early period after injury.

The Denver ED TOF score includes age, emergent intubation, hematocrit, EDSBP, blood urea nitrogen, and white blood cell count. The components of the score are clinically relevant and easily applied at the bedside. The successful use of the Denver ED TOF score in clinical practice would facilitate timely identification of patients in the early stages of MOF or identify those at risk for MOF early in the hospitalization. In these instances, aggressive targeted resuscitation and interventions could potentially be implemented to avert the development of MOF after trauma.

The Denver ED TOF score may also have the added benefit of serving as a useful and easily applied secondary triage instrument. The score could be used to identify patients at risk for MOF who may benefit from transfer to a Level 1 trauma center with a cadre of specialized trauma surgeons. Early transfer of these patients may facilitate prompt specialized surgical care and interventions that could potentially reduce the occurrence of MOF and improve outcomes. These strategies would improve the delivery of regionalized trauma care, potentially limit health care costs, and enhance regional health care resource use.

Before widespread implementation of this clinical predication tool, a large, prospective external validation is necessary. In the external validation, a heterogeneous trauma population will be necessary to determine the ability of the score to accurately predict the development of MOF in diverse populations. Once externally validated, the prediction rule may require evaluation in which clinical treatment is provided based on the probability assessed by the score, and an impact analysis is performed to assess the effects of the score on patient care.³²

The principal difficulty with this study is the use of a database not specifically designed for the study. This was a secondary analysis of a large, prospectively collected data set, and although predictors were collected in a way to facilitate our analysis of the data, they were

not collected specifically for this study. Since the model was developed and validated using this database, future investigations should focus on prospective clinical implementation of the score in a heterogeneous trauma population.

Since this was a retrospective study using trauma registry data, information on the number of patients who may have been intubated for altered mentation secondary to substance abuse and subsequently extubated was not available. It is possible that including patients in our population that were intubated for this reason may impact the specificity of the Denver ED TOF score. However, we believe the sensitivity of the score is of premium importance as compared with the specificity since the Denver ED TOF score will be used as a screening tool in the ED.

It is possible that there is an element of incorporation bias in this study, which may have influenced the performance of the prediction model. The variables in the prediction model may have been related to the primary outcome measure used to determine the development of MOF, the SOFA score. However, the laboratory data and clinical characteristics used to derive the prediction model and the SOFA score values used to determine the development of MOF in this study were measured at significantly different time intervals in each patient's hospital course. In addition, since the goal of this project was to develop a prediction tool for the development of MOF, it is anticipated that such a model would include laboratory data and clinical characteristics from several organ systems to predict the development of MOF.

We derived a simple and internally valid risk prediction tool to predict MOF in adults following trauma. The use of this score may allow early identification of patients at risk for MOF and result in targeted, goal-directed resuscitation and regionalized resource allocation in trauma. Prospective external validation in a large heterogeneous trauma population is required before widespread implementation of this decision rule in clinical practice.

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Figure 1.
Observed probability of MOF for the Denver ED TOF score.

Figure 2.
Calibration of the Denver ED TOF score (slope, 1.03; *dashed lines* represent 95% CIs).

Figure 3. Discrimination of the Denver ED TOF score (area under the curve, 0.92; 95% CI, 0.90–0.94).

Table 1
Demographics and Characteristics of the Study Sample

Variable	n	Percentage or Median (IQR)	Missing	
			n	%
Total, N	4,355			
Age, y	37	26–51	0	0
Male	3,146	72	2	0
Race/ethnicity			43	1
White	2,148	49		
Black	548	13		
Hispanic	1,492	34		
Other	124	3		
ISS	9	4–16	6	0
Mechanism				
Blunt	3,391	78	0	0
Penetrating, stab	358	8	0	0
Penetrating, gunshot	258	6	0	0
Other	348	8	0	0
Emergent intubation (prehospital or ED)	636	15	0	0
Prehospital total time, min	25	19–32	1,021	23
Prehospital response time, min	5	4–8	991	23
Prehospital scene time, min	10	7–14	996	23
Prehospital transport time, min	8	5–12	999	23
Prehospital vital signs				
Pulse	98	88–110	970	22
SBP	128	110–140	1,060	24
Respiratory rate	18	16–20	988	23
ED vital signs				
Pulse	92	80–106	24	1
SBP	130	116–146	27	1
Respiratory rate	18	16–20	83	2

Continuous data are expressed as median (IQR). IQR, interquartile range; ED, emergency department.

Table 2
Outcomes for the Study Sample

Variable	n = 4,355		
	n	Percentage *	95% CI
In-hospital mortality	138	3	3–4
MOF [†] within 7 d	216	5	4–6
Mortality	69	32	26–39
MOD [‡] within 7 d	1,161	27	25–28
Mortality	97	8	7–10
ICU admission	1,670	38	37–40
ICU LOS, median (IQR), d	2.5	1–8	2–3
Patients with <24-h ICU stay	589	35	33–38
Hospital LOS, median (IQR), d	4	2–7	4–4

IQR, interquartile range; MOD, multiple organ dysfunction; MOF, multiple organ failure; ICU, intensive care unit; SOFA score, Sequential Organ Failure Assessment score.

* Data are expressed as median (IQR) of subjects unless otherwise indicated.

[†] MOD defined as a score of 1 or higher in two or more systems as defined within the SOFA score.

[‡] MOF defined as a score of 3 or higher in two or more systems as defined within the SOFA score.

Table 3
Multivariable Logistic Regression Model and the Denver ED TOF Score for Prediction of
MOF* Following Acute Trauma in Adults (n = 4,355)

Predictor [†]	Regression Coefficient		Score [‡]
	β	95% CI	
Age 65 y	1.25	0.73–1.77	1
Emergent intubation [§]	3.11	2.72–3.49	3
Hematocrit			
Hematocrit < 20%	2.26	1.60–2.91	2
Hematocrit, 20% and <35%	1.29	0.93–1.64	1
Hematocrit 35%	Reference		
ED SBP < 90 mm Hg	0.50	0.05–0.96	1
Blood urea nitrogen 30 mg/dL	1.19	0.44–1.94	1
White blood cell count 20,000/ μ L	0.74	0.24–1.23	1

MOF, multiple organ failure; CI, confidence interval; SOFA, Sequential Organ Failure Assessment; ED, emergency department.

* MOF defined as a score of 3 or higher in two or more systems as defined within the SOFA score.

[†] The intercept for this model was –5.06.

[‡] Score calculated by rounding regression coefficient to the nearest integer.

[§] Emergent intubation defined as intubation occurring in the prehospital setting or in the ED.