Impact of comorbidities on the prognoses of trauma patients: Analysis of a hospital-based trauma registry database

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Abstract

Here we conducted a retrospective analysis of hospital-based trauma registry database for evaluating the impacts of comorbidities on the prognosis for traumatized patients using Index of Coexistent Comorbidity Disease (ICED) scores. We analyzed the data of patients with blunt trauma who visited emergency department between January 1, 2011, and December 31, 2015 in Chang-Gung Memorial Hospital, Keelung branch, a single level I trauma center in the Northern Taiwan. All consecutive patients with blunt trauma who admitted to the intensive care unit or ordinary ward after initial managements in the emergency department were included. We measured the hospital mortality of blunt traumatized patients using alive discharge as a competing risk. To investigate conditional independence of mortality and ICED scores given Injury Severity Score (ISS), we used log-linear models for modeling independence structures. Overall, we included 4997 patients (median age [IQR], 59 years old (44–75 years); 55.3% male). The mortality rate of blunt traumatized patients was higher in the higher ICED scores group compared to lower ICED scores group (4.7% vs 1.8%, \( p < 0.001 \)). Meanwhile, the higher ICED scores group were associated with older age, higher ISS, and longer hospital stay than lower ICED scores group. Higher ICED group had higher probability of transition-to-death and lower probability of transition-to-discharge under the competing risk model. In the multivariable analysis of transition-specific Cox models, higher ICED group were associated with higher risk for hospital mortality compared to lower ICED scores group (HR 1.60; [95% CI 1.04–2.47]; \( p = 0.032 \)). Also, higher ICED group were associated with lower probability of transition-to-discharge (HR 0.79; [95%CI 0.73–0.86]; \( p < 0.001 \)). Additionally, higher ICED scores accounted for hospital mortality among patients with ISS < 25. In conclusion, our study suggested that severity of comorbidity was associated with higher hospital mortality among traumatized patients, particularly lower ISS.
Introduction

Traumatic injury remains a major global public health problem and is associated with massive losses of health and life. According to the World Health Organization (WHO), unintentional injury is the sixth leading cause of death worldwide [1] and similarly, traumatic accidents represented the sixth-leading cause of death in Taiwan in 2016 [2]. Although advances in trauma care systems and vehicle and environmental safety have led to recent decreases in the overall mortality rate associated with trauma, diseases related to pre-existing diseases have increased significantly among elderly trauma patients [3–5].

Societies around the world are facing the issue of population aging. Accordingly, the average age of trauma patients is increasing, although younger patients still comprise the majority of victims [3, 5–7]. In Taiwan, the median age of trauma patient increased from 46 years in 2001 to 60 years in 2014 [2]. Given this trend toward population aging, trauma care systems are now faced with challenges related to the pre-existing comorbidities and impaired physiological reserves of elderly patients.

Several systems for scoring patient injuries are currently available. The Injury Severity Score (ISS) remains the mostly commonly used scoring system for predicting trauma severity and prognosis. The ISS was derived from the Anatomic Injury Score (AIS) but does not include the patient’s age and comorbidity [8]. Although, another predictive system, the Trauma and Injury Severity Score (TRISS), incorporates age, it fails to consider comorbidities [9, 10]. Only the Trauma Risk Adjustment Model (TRAM) incorporates comorbidities [11], however, this system accounts for the number but not the severity of comorbidities. The increasing prevalence of injury and the severity of comorbidities among elderly individuals indicate the need for a scoring system that would consider not only the number but also the severity of comorbidities, as these factors affect traumatic outcomes and thus impact long-term survival [12].

Many clinical scores have been developed to measure or quantify comorbidities. The most prevalent of these scores is the Charlson Index, which includes 19 weighted disease items [13]. Other similar comorbidity measuring scores, such as the Cumulative Illness Rating Scale (CIRS) [14], Geriatric Index of Comorbidity (GIC) [15], Comorbidity-Polypharmacy Score [16], Index of Coexistent Comorbidity Disease (ICED) [17], and Kaplan Index use similar methods to quantify comorbidity. Among these, ICED considers both pre-existing diseases, as well as the overall functional disability caused by comorbidities [18]. Here, we conducted a hospital-based cohort study and competing risk model to investigate the impacts of the ICED scores of trauma patients on hospital outcomes. In addition, we investigated the association between mortality and ICED scores conditional on ISS.

Materials and methods

Study design

For this study, we retrospectively analyzed the hospital trauma registry database, which we prospectively registered consecutive trauma patients visiting our emergency department at Chang Gung Memorial hospital, Keelung, a single level I trauma center in North Taiwan, between January 1, 2011 and December 31, 2015. All patients with blunt traumatic injury who were admitted to the intensive care unit or ordinary ward after primary surveillance in the emergency department were enrolled in this study; however, patients with penetrating injuries, burns, out-hospital cardiac arrest (OHCA), an incomplete medical history, an age younger than 20 years, and discharge or death within 24 hours of admission were excluded. We collected the following data for all patients: demographic information, admission duration, vital
signs (blood pressure, respiratory rate) and Glasgow coma scale (GCS) at triage, ISS score, number of comorbidities, and discharge condition. All baseline and demographic, including age, sex, GCS, systolic blood pressure (SBP), heart rate (HR), respiratory rate (RR), ISS, history of ICU admission, number of comorbidities, ICED score, and length of hospital stay were recorded. This study was approved by the institutional review board of Chang Gung Memorial Hospital. (IRB approval number:201701589B0D001)

**Assessment of patients’ comorbidities**

We used the ICED score to evaluate comorbidities [19, 20]. This score is derived from two separate assessments: the Index of Disease Severity (IDS), which comprises 19 medical conditions (each defined by 4 severity levels), and the Index of Physical Impairment (IPI), which comprises 11 physical impairments (each defined by 3 severity levels). The final ICED scores, which range from 0 to 3 in four classes (normal, mild, moderate, severe), are calculated using an algorithm that combines the single highest (“peak”) IDS score with the peak IPI score. In the current study, we defined ICED scores of 0–1 and 2–3 as minor and severe comorbidity, respectively. To ensure the accurate scoring of comorbidities, ICED scores were calculated by two researchers (Ti-Hsuan Chien and Hao-Yu Chang); a third researcher (Yu-Hsien Chen) was consulted to resolve discrepancies.

**Statistical analysis**

Continuous variables are presented as medians with interquartile ranges (IQRs) for non-normality, whereas categorical variables are presented as frequencies and percentages. According to the independence assumption in the Cox model, the hazard of the individuals that are censored is equal to the hazard of the individuals that remain in follow-up. In the presence of a competing risk, alive discharge prevents the occurrence of hospital mortality. Thus, the independence assumption is not satisfied. If we had not accounted for competing events, we would have overestimated the cumulative incidence of hospital mortality [21–24]. Thus, we used the competing risk model to investigate the impacts of two levels of ICED scores, with alive discharge as a competing event for hospital mortality.

Additionally, cause-specific Cox models were used to investigate the predictors of two events. The Akaike information criterion (AIC) and substantive knowledge were used for model selection and to identify parsimonious models, respectively. We further investigated the proportional hazards assumption using the modified Schoenfeld residuals test; here, if the proportional hazards assumptions were not met, we investigated the non-linear effects of continuous variables and used time-dependent variables to fit the Cox model [25, 26].

To investigate conditional independence of mortality and ICED scores given ISS, we used log-linear models for modeling independence structures [27] and mosaic plots for bringing them out graphically [28,29]. Mosaic plots have been illustrated in the literature to be an excellent means of visualization for log-linear models to display complete, joint or conditional independence of categorical data. For all of these hypotheses, tables of estimated expected values and residuals (Pearson or deviance) can be computed for hypothesis testing. For inference, the most commonly used aggregation function for the residuals is the sum of squares yielding the associated Pearson or likelihood ratio statistic, respectively [27]. Friendly et al. have showed that residual-based shading scheme can directly be applied to these more complex independence models [28,29]. All confidence intervals (CIs) and tests were two-sided with a significance level of 5%. For the log-linear model, Pearson residuals are standardized deviations of observed from expected values. The heuristic for choosing the cut-off points 2 and 4 is that the Pearson residuals are approximately standard normal distribution, which implies that the
highlighted cells are those with residuals individually significant at approximately the alpha = 0.05 and alpha = 0.0001 levels, respectively [30]. All analyses were performed using R software, version 3.4.3 (R Foundation for Statistical Computing, Vienna, Austria) with contributed packages “mstate”, “survival”, and “vcd”. Raw data and computer codes were provided in the supportive information (S1 File, S2 Table, and S2 File).

**Result**

A total of 6012 blunt trauma patients were initially selected from our Trauma Registry database. Of these patients, 604 (10%) with ages younger than 20 years and 362 (6%) who died within 24 hours were excluded, as were 43 with missing medical histories and 6 with missing ISSs. Finally, 4997 patients were enrolled in the analysis (S1 Fig). Among them, 4153 (83.1%) were classified as ICED 0 or 1 (i.e., lower ICED), and 844 (16.9%) as ICED 2 or 3 (higher ICED), according to the calculation algorithm. The median age of all patients was 59 years old (IQR: 44–75 years) (S1 Table). Furthermore, 766 (15.3%) patients had ISS scores >15 and 695 (13.9%) were admitted to the ICU.

Table 1 showed the patient’s characteristics stratified by ICED scores. Compared to with the lower ICED group, the higher ICED group tended to include older and female patients with higher ISS, and had a significantly longer hospital stay than the lower ICED group (9 vs. 7 days, p < 0.001). Meanwhile, the higher ICED group also had a significantly higher mortality rate than the lower group (4.7% vs. 1.8%, p < 0.001).

Fig 1 presents the cumulative hazards for the transition-to-death and transition-to-discharge in the competing risk model, stratified by ICED scores. The higher ICED group had a higher probability of transition-to-death when compared with the lower ICED group (Table 2), while the “transition-to-death” probability in the latter plateaued after 20 days of admission. We next conducted a multivariable analysis using transition-specific Cox models.

### Table 1. Patient characteristics stratified by Index of Coexisting Disease scores.

| Index of Coexisting Disease category | Lower (ICED 0,1) (n = 4153) | Higher (ICED 2,3) (n = 844) | p value |
|-------------------------------------|-----------------------------|-----------------------------|---------|
| Sex, Male (%)                       | 2404 (57.9)                 | 357 (42.3)                  | < 0.001 |
| Age, median (IQR), years            | 56 (41, 70)                 | 79 (69, 85)                 | < 0.001 |
| GCS < 13 (%)                        | 287 (6.9%)                  | 68 (8.1%)                   | 0.268   |
| SBP, median (IQR), mmHg             | 141 (124, 160)              | 149 (128, 170)              | 0.807   |
| ISS, median (IQR)                   | 9 (4, 9)                    | 9 (9, 9)                    | < 0.001 |
| ISS < 16                            | 3534 (85.1)                 | 697 (82.6)                  | 0.129   |
| 16 < ISS < 25                       | 417 (10.0)                  | 94 (11.1)                   |         |
| 25 ≤ ISS                            | 202 (4.9)                   | 53 (6.3)                    |         |
| ICU admission (%)                   | 585 (14.1)                  | 110 (13.0)                  | 0.452   |
| Admission days, median (IQR), d     | 7 (4, 12)                   | 9 (6, 15)                   | < 0.001 |
| No. of comorbidities (%)            |                             |                             |         |
| 0                                   | 2457 (59.2)                 | 26 (3.1)                    | < 0.001 |
| 1                                   | 917 (22.1)                  | 263 (31.2)                  |         |
| 2                                   | 627 (15.1)                  | 330 (39.1)                  |         |
| ≥3                                  | 152 (3.7)                   | 225 (26.7)                  |         |
| Death (%)                           | 74 (1.8%)                   | 40 (4.7%)                   | < 0.001 |

ICED = Index of Coexisting Disease. IQ = interquartile. GCS = Glasgow coma scale. SBP = systolic blood pressure. ISS = injury severity score. ICU = intensive care unit.

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to investigate the predictors of transition-to-death and transition-to-discharge (Table 3). Compared to the lower ICED group, the higher ICED group had a significantly higher transition-to-death risk after adjusting for age, GCS, ICU admission, and ISS (hazard ratio [HR]: 1.60; 95% CI: 1.04–2.47; \( p = 0.032 \)). Notably, an older age, GCS <13, and ICU admission were also significantly associated with a higher risk of transition-to-death, whereas the ISS had a non-linear effect on this outcome (Fig 2). However, the higher ICED group had a lower potential for transition-to-discharge after adjusting for age, sex, GCS, ICU admission, SBP, and ISS (HR: 0.79; 95% CI: 0.73–0.86; \( p < 0.001 \)). An older age, GCS <13, and ICU admission were

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**Fig 1. Cumulative hazards stratified by the ICED scores in the competing risk model.** Orange lines indicated lower ICED group (n = 4153) whereas blue lines represented higher ICED group (n = 844). Higher ICED group had higher cumulative hazards for transition-to-death and lower cumulative hazards for transition-to-discharge compared with lower ICED group.

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significantly associated with a lower potential for transition-to-discharge, and ICU admission had a time-dependent effect on this outcome; specifically, comparing to patients without ICU admission, those with ICU admission of <10 days had a HR of 0.39 for transition-to-discharge in the multivariate analysis (p < 0.001). And, comparing to patients without ICU admission, those with ICU admission of 10–30 days had a HR of 0.60 for transition-to-discharge (p < 0.001). Further, male sex correlated significantly with a lower potential for transition-to-discharge after 10 days of admission. Finally, ISS and SBP had non-linear effects on transition-to-discharge (Fig 2).

The mosaic plot of log-linear model showed that patients with higher ICED score were significantly associated with increased mortality counts than expected (positive Pearson residuals) for trauma patients with ISS <16 and patients with 16 ≤ ISS < 25 (Fig 3). Conversely, the cell of lower ICED score and ISS < 16 had significant lower mortality counts than the expected value (negative Pearson residuals).

### Table 2. Twenty-, 40-, and 60-day state-occupied probabilities in the competing risk model.

| Comorbidity index | Status       | State-occupied probability (95% CI) |
|-------------------|--------------|-----------------------------------|
|                   |              | 20-day                            | 40-day                  | 60-day                  |
| ICED 0/1          | Admission    | 9.2 (8.3–10.1)                    | 2.3 (1.8–2.8)           | 0.8 (0.5–1.1)           |
| ICED 0/1          | Death        | 1.6 (1.2–2.0)                     | 1.8 (1.4–2.2)           | 1.8 (1.4–2.2)           |
| ICED 0/1          | Discharge    | 89.2 (88.3–90.2)                  | 96.0 (95.3–96.6)        | 97.4 (97.0–97.9)        |
| ICED 2/3          | Admission    | 15.1 (12.6–17.5)                  | 4.7 (3.2–6.2)           | 2.0 (1.0–3.0)           |
| ICED 2/3          | Death        | 4.1 (2.7–5.4)                     | 4.3 (2.9–5.7)           | 4.6 (3.2–6.0)           |
| ICED 2/3          | Discharge    | 80.9 (78.2–83.5)                  | 91.0 (89.0–93.0)        | 93.5 (91.8–95.2)        |

ICED = Index of Coexisting Disease. CI = confidence interval.

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### Table 3. Multivariable analysis of transition-specific Cox models.

| Variables          | Category               | HR (95% CI)   | p value |
|--------------------|------------------------|---------------|---------|
| Transition to death|                        |               |         |
| Age                | 10-year increments     | 1.38 (1.22–1.56) | < 0.001 |
| GCS                | Every point increase   | 0.84 (0.80–0.88) | < 0.001 |
| ICU admission      | No                     | 1             |         |
|                    | Yes                    | 3.19 (1.60–6.34) | <0.001  |
| ICED               | Lower                  | 1             |         |
|                    | Higher                 | 1.60 (1.04–2.47) | 0.032   |
| Transition to discharge |                |               |         |
| Age                | 10-year increments     | 0.98 (0.96–0.99) | 0.008   |
| GCS                | Every point increase   | 1.04 (1.02–1.06) | < 0.001 |
| ICED               | Lower                  | 1             |         |
|                    | Higher                 | 0.79 (0.73–0.86) | < 0.001 |
| ICU admission      | < 10 days              | Yes vs. No    | 0.39 (0.33–0.46) | < 0.001 |
|                    | 10–30 days             | Yes vs. No    | 0.60 (0.52–0.71) | < 0.001 |
|                    | > 30 days              | Yes vs. No    | 0.88 (0.66–1.18) | 0.398   |
| Sex                | < 10 days              | Male vs. Female | 0.98 (0.91–1.05) | 0.493   |
|                    | ≥ 10 days              | Male vs. Female | 0.79 (0.71–0.87) | < 0.001 |

HR = hazard ratio. CI = confidence interval. ICED = Index of Coexisting Disease. GCS = Glasgow coma scale.

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Discussion

In our study, which incorporated information about comorbidities via the ICED scoring system, we found that an increase in the severity of comorbidities was associated with a poor prognosis among patients with blunt trauma in the competing risk model. In addition, in the log-linear model investigating conditional independence of mortality and ICED scores given ISS, trauma patients with higher ICED scores accounted for mortality among patients with ISS < 16.

Traditionally, the TRISS system [31], which incorporates the ISS for evaluating the severity of anatomic injuries and RTS for evaluating physiologic responses and patient age as a measure of physiologic reserve, has been used to estimate the survival probabilities of trauma patients. Subsequently, Bergeron et al [32] developed the TRISSCOM model, which redefines the age category and adds comorbidities to the TRISS model. The TRISSCOM system includes comorbidity as a binary variable that includes only eight conditions. However, few studies have investigated the effects of comorbidity severity and individual physical activity on trauma outcomes. To the best of our knowledge, our study is the first one to clarify these impacts.

In addition to the paucity of general information about the impacts of comorbidities, no standard or uniform method existed for the evaluation or quantification of comorbidity severity in elderly traumatized patients. Recently, some studies investigated whether incorporating comorbidity and polypharmacy data would improve abilities to predict the mortality outcomes.
of elderly trauma patients [15, 16, 18, 33]. In addition, the TRAM, developed by Lynne et al [11], incorporates the number of comorbidities and thus yields a superior prediction performance, compared to the TRISS model. Still, although TRAM improved prediction accuracy, it failed to account for comorbidity severity. In the current study, therefore, we used ICED scores as a measure of comorbidity severity and physical impairments in our patient sample. As noted previously, a patient’s physiologic reserve and comorbidity-related responses, rather than age or the number of comorbidities, were found to associate with outcomes [34, 35]. Future studies are recommended to investigate predicting performance incorporating different comorbidity scoring systems, and to create new coding algorithms specific for trauma patients.

The commonly used TRISS system dichotomizes patient age at 55 years. However, this approach compromised the validity of outcome predictions in an aging population [36]. This is a significant concern because advances in medical and surgical care are expected to increase the average human lifespan. Accordingly, we are approaching a “geriatric era”, wherein the field of traumatology will gradually transition to a geriatric science [3]. For example, in the Major Trauma Outcome Study (MTOS) of 1987, trauma patients older than 55 years accounted for only 15.5% of the sample [10], whereas in the current study, half of the trauma patients were older than 55 years, and one-third were older than 70 years. We note that this increase in the age of the trauma population also occurred in other studies, despite differences

**Fig 3.** Mosaic plot visualizing the distribution of mortality and ICED scores given ISS using the log-linear model. The size of each cell is proportional to the observed frequency. The Pearson residuals are standardized deviations of observed from expected values. The cut-off points 2 and 4 implies that the highlighted cells are those with residuals individually significant at approximately the alpha = 0.05 and alpha = 0.0001 levels, respectively. Each colored residual violates the null hypotheses of independence. Light blue colored cell indicates positive Pearson residuals at alpha = 0.05 level. Dark blue colored cell indicates positive Pearson residuals at alpha = 0.0001 level. Red colored cell represents negative Pearson residuals at alpha = 0.05 level. The p value is for the log-linear model investigating conditional independence of mortality and ICED scores given ISS, which is highly significant.

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in the definitions of elderly patients [37–41]. However, it seems impractical to define a clear age cut-off because differences in comorbidities will lead to differences in actual physiological changes and the ability to recover from major trauma, even among patients of the same age [42].

In the present study, the observed association of a higher ICED score with an older age is straightforward, as elderly patients tend to have more comorbidities and physical impairments. We also note that patients in the higher ICED group also had relatively higher ISSs; however, there was not statistically significant stratified by ISSs. In addition, ICU admission was not statistically significant between 2 groups. The possible reason might be our inclusion criteria. We included patients surviving more than 24 hours of admission. Patients with higher ICED and ISSs might suffer from unfavorable outcomes earlier.

For our investigation of prognostic factors, we selected a competing risk model that included nonlinear and time-dependent effects for several reasons. First, most studies of the impacts of comorbidities on trauma patients used a logistic regression model [12, 33, 43] that only reflected the risk factors for transition-to-death. However, a single variable might have different effects on different transitions in the presence of competing risks. Second, transition-specific Cox models can be used to investigate time-dependent effects when the proportional hazards assumption is not hold. In addition, this approach allowed us to calculate the state-occupied probability during the period of hospital admission, which better reflected the real-world situation over time [44]. In the “transition to death” situation, patients with higher ICED scores had higher mortality throughout the admission period, whereas all mortality among the lower ICED group occurred within 20 days. These results suggest that early mortality in the lower ICED group could be attributed to a higher ISS, whereas both early and late mortality in the higher ICED group were influenced by the ISS and comorbidities. Despite improvements in early mortality (e.g., exsanguination), the rate of late mortality, or events occurring beyond 1 week after trauma, remained unchanged [45]. In one study reporting a late mortality rate of 2.36%, 38.69% of these cases involved victims older than 71 years [46]. These late mortality events often involve sepsis and multi-organ failure associated with the complications of trauma and the patient’s comorbidities. These results are consistent with our log-linear model that higher ICED score accounted for mortality for patients with lower ISS.

In addition to comorbidity, several known risk factors associated with admission-to-death and admission-to-discharge were identified. In contrast to other studies [47, 48], we observed non-linear relationships of ISS with “admission to death” and “admission to discharge”. The relationship of SBP with the transition-to-discharge transition was also non-linear. Interestingly, we observed a significant association of the male sex with a lower potential for transition-to-discharge. As we also observed significant associations of the male sex with a lower GCS, increased likelihood of ICU admission, and lower comorbidity scores, the sex-based effects might be driven by a combination of all these factors.

The present study had several limitations of note. First, a higher ICED score was found to associate with age, sex, and ISS. Therefore, we could not exclude the effects of these potential confounders on comorbidities. Second, we did not thoroughly compare all comorbidity scoring systems into the prediction models. Indeed, there is no consensus exists regarding the coding of comorbidities in traumatized patients. Therefore, further studies of this topic are warranted. In addition, comparing different comorbidity scoring systems in the prediction performance for traumatized patients is important as well. Finally, our study was conducted at a single-center, which might influence the external validity and generalizability of our findings.
Conclusion
Our study suggested that severity of comorbidity was associated with higher hospital mortality among traumatized patients. In addition, higher ICED scores accounted for mortality among traumatized patients with ISS < 25, particularly among patients with ISS < 16.

Supporting information
S1 Fig. Flow chart of the patient selection process.
(TIF)
S1 File.
(CSV)
S2 File.
(PDF)
S1 Table. Baseline patient demographics and characteristics.
(DOCX)
S2 Table. Data description.
(DOCX)

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References
1. Organization, WH. Global Burden of Disease. http://www.who.int/healthinfo/global_burden_disease/en/ accessed 28 February 2018
2. Ministry of Health and Welfare, Taiwan. 2016 Statistics of Causes of Death June,2016. Available from: https://dep.mohw.gov.tw/DOS/tp-3352-113.html accessed 28 February 2018
3. Kahl JE, Calvo RY, Sise MJ, Sise CB, Thordike JF, Shackford SR. The changing nature of death on the trauma service. J Trauma Acute Care Surg. 2013; 75(2):195–201. Epub 2013/07/05. https://doi.org/10.1097/TA.0b013e3182997865 PMID: 23823614.
4. Glance LG, Osler TM, Mukamel DB, Dick AW. Outcomes of adult trauma patients admitted to trauma centers in Pennsylvania, 2000–2009. Arch Surg. 2012; 147(8):732–7. Epub 2012/08/23. https://doi.org/10.1001/archsurg.2012.1138 PMID: 22911068.
5. Kuhne CA, Ruchholtz S, Kaiser GM, Nast-Kolb D. Mortality in severely injured elderly trauma patients—when does age become a risk factor? World J Surg. 2005; 29(11):1476–82. Epub 2005/10/18. https://doi.org/10.1007/s00268-005-7796-y PMID: 16228923.
6. Rihee P, Joseph B, Pandit V, Aziz H, Vercruysse G, Kulvatunyou N, et al. Increasing trauma deaths in the United States. Ann Surg. 2014; 260(1):19–21. https://doi.org/10.1097/SLA.0000000000000600 PMID: 24651132
7. Dutton RP, Stansbury LG, Leone S, Kramer E, Hess JR, Scalea TM. Trauma mortality in mature trauma systems: are we doing better? An analysis of trauma mortality patterns, 1997–2008. J Trauma. 2010; 69(3):620–6. Epub 2010/01/23. https://doi.org/10.1097/TA.0b013e3181bb862a PMID: 20093983.
8. Lefering R. Trauma scoring systems. Curr Opin Crit Care. 2012; 18(6):637–40. Epub 2012/08/25. https://doi.org/10.1097/MCC.0b013e3283585356 PMID: 22918259.
9. Champion HR, Copes WS, Sacco WJ, Frey CF, Holcroft JW, Hoyt DB, et al. Improved predictions from a severity characterization of trauma (ASCOT) over Trauma and Injury Severity Score (TRISS): results of an independent evaluation. J Trauma. 1996; 40(1):42–8; discussion 8–9. Epub 1996/01/01. PMID: 8576997.

10. Champion HR, Copes WS, Sacco WJ, Lawnick MM, KEAST SL, FREY CF. The Major Trauma Outcome Study: establishing national norms for trauma care. J Trauma. 1990; 30(11):1356–65. PMID: 2231804

11. Moore L, Lavoie A, Turgeon AF, Abdous B, Le Sage N, Emond M, et al. The trauma risk adjustment model: a new model for evaluating trauma care. Ann Surg. 2009; 249(6):1040–6. https://doi.org/10.1097/SLA.0b013e3181a6cd97 PMID: 19474674

12. Holmes M, Garver M, Albrecht L, Arbabi S, Pham TN. Comparison of two comorbidity scoring systems for older adults with traumatic injuries. J Am Coll Surg. 2014; 219(4):631–7. Epub 2014/08/27. https://doi.org/10.1016/j.jamcollsurg.2014.05.014 PMID: 25154672.

13. Quan H, Sundararajan V, Halfon P, Fong A, Burnand B, Luthi JC, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. Med Care. 2005; 43(11):1130–9. Epub 2005/10/15. PMID: 16224307.

14. Linn BS, Linn MW, Gurel L. Cumulative illness rating scale. J Am Geriatr Soc. 1968; 16(5):622–6. Epub 1968/05/01. PMID: 5646906.

15. Zekry D, Loures Vallee BH, Lardi C, Graf C, Michel J-P, Gold G, et al. Geriatrics index of comorbidity was the most accurate predictor of death in geriatric hospital among six comorbidity scores. J Clin Epidemiol. 2010; 63(9):1036–44. https://doi.org/10.1016/j.jclinepi.2009.11.013 PMID: 20236800

16. Evans DC, Cook CH, Christy JM, Murphy CV, Gerlach AT, Eiferman D, et al. Comorbidity-Polypharmacy Scoring Facilitates Outcome Prediction in Older Trauma Patients. J Am Geriatr Soc. 2012; 60(8):1465–70. https://doi.org/10.1111/j.1532-5415.2012.04075.x PMID: 22786874.

17. Greenfield S, Apolone G, McNeil BJ, Cleary PD. The importance of co-existent disease in the occurrence of postoperative complications and one-year recovery in patients undergoing total hip replacement. Med Care. 1993; 31(2):141–54. Epub 1993/02/01. PMID: 8435577.

18. de Groot V, Beckerman H, Lankhorst GJ, Bouter LM. How to measure comorbidity: a critical review of available methods. J Clin Epidemiol. 2003; 56(3):221–9. PMID: 12725876

19. Miskulin DC, Athienitis NV, Yan G, Martin AA, Ornt DB, Kusek JW, et al. Comorbidity index of severity was the most accurate predictor of death in geriatric hospital among six comorbidity scores. J Clin Epidemiol. 2001; 54(4):1498–510. Epub 2001/09/29. https://doi.org/10.1016/S0895-4356(01)00051-8 PMID: 11576365.

20. Greenfield S, Sullivan L, Dukes KA, Stillman R, D’Agostino R, Kaplan SH. Development and testing of a new measure of case mix for use in office practice. Medical care. 1995:AS47–AS55. PMID: 7723461

21. Wolkwitz M, Cooper BS, Bonten MJ, Barnett AG, Schumacher M. Interpreting and comparing risks in the presence of competing events. BMJ (Clin Res ed). 2014; 349:g5060. Epub 2014/08/26. https://doi.org/10.1136/bmj.g5060 PMID: 25146097.

22. Grambauer N, Schumacher M, Deltenkofer M, Beyersmann J. Incidence densities in a competing events analysis. Am J Epidemiol. 2010; 172(9):1077–84. Epub 2010/09/08. https://doi.org/10.1093/aje/kwp246 PMID: 20817786.

23. Lau B, Cole SR, Gange SJ. Competing risk regression models for epidemiologic data. Am J Epidemiol. 2009; 170(2):244–56. Epub 2009/06/06. https://doi.org/10.1093/aje/kwp107 PMID: 19494242; PubMed Central PMCID: PMCPMC2732996.

24. de Wreede LC, Fiocco M, Putter H. mstate: R Package for the Analysis of Competing Risks and Multi-State Models. J Stat Softw. 2011; 38(7):30. Epub 2011-01-04. https://doi.org/10.18637/jss.v038.i07

25. Therneau Terry M. Modeling Survival Data: Extending the Cox Model: Springer, New York, NY; 2000.

26. Licht AA. Change Comes with Time: Substantive Interpretation of NonProportional Hazards in Event History Analysis. Polit Anal. 2011; 19(2):227–43.

27. Agresti A. Categorical data analysis: John Wiley & Sons; 2013.

28. Friendly M. Mosaic displays for multi-way contingency tables. Journal of the American Statistical Association. 1994; 89(425):190–200.

29. Friendly M. Extending mosaic displays: Marginal, conditional, and partial views of categorical data. Journal of Computational and graphical Statistics. 1998; 8(3):373–95.

30. Zeileis A, Meyer D, Hornik K. Residual-based shadings for visualizing (conditional) independence. Journal of Computational and Graphical Statistics. 2007; 16(3):507–25.
31. Boyd CR, Tolson MA, Copes WS. Evaluating trauma care: the TRISS method. J Trauma. 1987; 27(4):370–8. PMID: 3106646
32. Bergeron E, Rossignol M, Osler T, Cias D. Improving the TRISS methodology by restructuring age categories and adding comorbidities. J Trauma. 2004; 56(4):760–7. PMID: 15187738
33. Mubang RN, Stoltzfus JC, Cohen MS, Hoey BA, Stehly CD, Evans DC, et al. Comorbidity-polypharmacy score as predictor of outcomes in older trauma patients: A retrospective validation study. World J Surg. 2015; 39(8):2068–75. Epub 2015/03/27. https://doi.org/10.1007/s00268-015-3041-5 PMID: 25809063.
34. Mulrow CD, Gerety MB, Cornell JE, Lawrence VA, Kanten DN. The relationship between disease and function and perceived health in very frail elders. J Am Geriatr Soc. 1994; 42(4):374–80. Epub 1994/04/01. PMID: 8144821.
35. Kauder D. The geriatric puzzle. Assessment challenges of elderly trauma patients. JEMS. 2000; 25(7):64–6, 8–70, 2–4. PMID: 11183107
36. Grossman MD, Miller D, Scaff DW, Arcona S. When is an elder old? Effect of preexisting conditions on mortality in geriatric trauma. J Trauma. 2002; 52(2):242–6. PMID: 11834982
37. Rogers FB, Osler TM, Shackford SR, Morrow PL, Sartorelli KH, Camp L, et al. A population-based study of geriatric trauma in a rural state. J Trauma. 2001; 50(4):604–11. PMID: 11303153
38. Taylor MD, Tracy JK, Meyer W, Pasquale M, Napolitano LM. Trauma in the elderly: intensive care unit resource use and outcome. J Trauma. 2002; 53(3):407–14. https://doi.org/10.1097/01.TA.0000020257.29911.70 PMID: 12352472
39. Perdue PW, Watts DD, Kaufmann CR, Trask AL. Differences in mortality between elderly and younger adult trauma patients: geriatric status increases risk of delayed death. J Trauma. 1998; 45(4):805–10. PMID: 9783625
40. Caterino JM, Valasek T, Werman HA. Identification of an age cutoff for increased mortality in patients with elderly trauma. Am J Emerg Med. 2010; 28(2):151–6. Epub 2010/02/18. https://doi.org/10.1016/j.ajem.2008.10.027 PMID: 20159383.
41. Campbell-Furtick M, Moore BJ, Overton TL, Laureano Phillips J, Simon KJ, Gandhi RR, et al. Post-trauma mortality increase at age 60: a cutoff for defining elderly? Am J Surg. 2016; 212(4):781–5. Epub 2016/04/04. https://doi.org/10.1016/j.amjsurg.2015.12.018 PMID: 27038794.
42. Hashmi A, Ibrahim-Zada I, Rhee P, Aziz H, Fain MJ, Friese RS, et al. Predictors of mortality in geriatric trauma patients: a systematic review and meta-analysis. J Trauma Acute Care Surg. 2014; 76(3):894–901. Epub 2014/02/21. https://doi.org/10.1097/TA.0b013e3182ab0763 PMID: 24553567.
43. Skaga NO, Eken T, Jones JM, Steen PA. Different definitions of patient outcome: consequences for performance analysis in trauma. Injury. 2008; 39(5):612–22. Epub 2008/04/02. https://doi.org/10.1016/j.injury.2007.11.426 PMID: 18377909.
44. Jepsen P, Vilstrup H, Andersen PK. The clinical course of cirrhosis: The importance of multistate models and competing risks analyses. Hepatology. 2015; 62(1):292–302. Epub 2014/11/08. https://doi.org/10.1002/hep.27598 PMID: 25376655.
45. Eriksson M, Brattstrom O, Larsson E, Oldner A. Causes of excessive late death after trauma compared with a matched control cohort. Br J Surg. 2016; 103(10):1282–9. Epub 2016/07/29. https://doi.org/10.1002/bjs.10197 PMID: 27465211.
46. Valdez C, Sarani B, Young H, Amdur R, Dunne J, Chawla LS. Timing of death after traumatic injury—a contemporary assessment of the temporal distribution of death. J Surg Res. 2016; 200(2):604–9. Epub 2015/10/24. https://doi.org/10.1016/j.jss.2015.08.031 PMID: 26494012.
47. Osler T, Baker SP, Long W. A modification of the injury severity score that both improves accuracy and simplifies scoring. J Trauma. 1997; 43(6):922–6. discussion 5–6. Epub 1998/01/07. PMID: 9420106.
48. Tohira H, Jacobs I, Mountain D, Gibson N, Yeo A. Systematic review of predictive performance of injury severity scoring tools. Scand J Trauma Resusc Emerg Med. 2012; 20:63. Epub 2012/09/12. https://doi.org/10.1186/1757-7241-20-63 PMID: 22964071; PubMed Central PMCID: PMCPMC3511252.