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Original Contribution

Quantifying the burden of pre-existing conditions in older trauma patients: A novel metric based on mortality risk [☆]Richard Y. Calvo, PhD ^{a,b,*}, C. Beth Sise, MSN ^a, Michael J. Sise, MD ^a, Vishal Bansal, MD ^a^a Scripps Mercy Hospital, Trauma Services, 4077 Fifth Avenue, San Diego, CA 92103, USA^b SDSU/UCSD Joint Doctoral Program in Public Health (Epidemiology), 5500 Campanile Drive, San Diego, CA, 92182, USA

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ABSTRACT

Introduction: Pre-existing medical conditions (PEC) represent a unique domain of risk among older trauma patients. The study objective was to develop a metric to quantify PEC burden for trauma patients. **Methods:** A cohort of 4526 non-severe blunt-injured trauma patients aged 55 years and older admitted to a Level I trauma center between January 2006 and December 2012 were divided into development (80%) and test (20%) sets. Cox regression was used to develop the model based on in-hospital and 90-day mortality. Regression coefficients were converted into a point-based PEC Risk Score. Performance of the PEC Risk Score was compared in the test set with two other PEC-based metrics and three injury-based metrics. An external cohort of 2284 trauma patients admitted in 2013 was used to evaluate combined metric performance.

Results: Total mortality was 9.4% and 9.1% in the development and test set, respectively. The final model included 12 PEC. In the test set, the PEC Risk Score (c-statistic: 79.7) was superior for predicting in-hospital and 90-day mortality compared with all other metrics. For in-hospital mortality alone, the PEC Risk Score similarly outperformed all other metrics. Combination of the PEC Risk Score and any injury-based metric significantly improved prediction compared with any injury-based metric alone.

Conclusion: Our 12-item PEC Risk Score performed well compared with other metrics, suggesting that the classification of trauma-related mortality risk may be improved through its use. Among non-severely injured older trauma patients, the utility of prognostic metrics may be enhanced through the incorporation of comorbidities.

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1. Introduction

Older injured patients constitute a rapidly growing segment of the U.S. trauma center population. In addition to the complications of injury, older trauma patients suffer from pre-existing medical conditions (PEC), age-related functional decline, and reductions in physiologic reserve [1–6]. As a result, these complex patients incur worse outcomes for a given severity of injury than their younger counterparts [7–9]. Moreover, those who survive to discharge remain at a significant risk for death in the months following discharge [10–12].

Previous studies of mortality in trauma patients have indicated that the relevant risk factors are more associated with aging, notably PEC, than with injury [2–5,11,12]. However, two metrics widely used to benchmark performance of U.S. trauma centers, the Trauma and Injury Severity Score (TRISS) and the Revised Trauma Score (RTS), are based on degree of anatomic injury and altered physiology, and do not account for PEC that may affect mortality [13,14]. Studies have demonstrated a diminished applicability of TRISS and RTS to accurately predict mortality in trauma populations which may be attributed to an absence of a PEC domain [15–23]. Despite these attempts, the PEC domain remains inadequately defined in trauma patients.

A recent report noted that PEC, in general, affected mortality in older trauma patients [24]. However, no specific PEC were articulated. To address this gap in the literature, we conducted a study to identify the PEC that best predict mortality following injury in older trauma patients. Objectives of this study were to develop and explore the validity of a prognostic mortality risk-scoring tool based on PEC that is specific to trauma patients. Secondary aims were to compare the validity of our new PEC Risk Score to several widely-used prognostic metrics.

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2. Materials and methods

2.1. Study population

This study was approved by the Scripps Institutional Review Board. Blunt-injured trauma patients aged 55 years and older admitted to an urban Level I trauma center in California between January 2006 and December 2012 were selected for this study. Although an age of 65 years has been recommended as the threshold to define the geriatric trauma patient, there is significant support for using an age of 55 years with comorbidities [24]. In addition, the age threshold of 55 years was selected based on previous studies that demonstrated an elevated mortality risk among patients at and above this age [13,25]. Furthermore, the national trauma triage criteria uses the age of 55 as a criterion for transport to a trauma center owing to the perceived increased mortality risk in this group [26,27].

Exclusions were made for patients with a hospital length of stay less than 6 h ($n = 311$), those with a probability of death $>50\%$ ($n = 92$) based on anatomic injury assessed by the Trauma Mortality Prediction Model (TMPM) [28], and those with significant missing data that prevented matching to external data sources ($n = 35$). The primary cohort consisted of 4526 patients met all inclusion criteria. A secondary cohort of 2284 trauma patients aged 18 years or older admitted during the 2013 calendar year with blunt or penetrating injury and with a hospital length of stay over 6 h was retained as to evaluate external validity (external test set).

2.2. Study variables

Primary data were extracted from the trauma registry and included patient identifiers, injury-related characteristics, vital signs, procedures, discharge status, discharge location, and length of stay. The hospital administrative database provided a secondary data source for discharge status, insurance information, and International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes. Individual PEC were selected for study based on their documentation in the trauma registry (Appendix A, Table A1). For each PEC, the hospital administrative database was scanned for the relevant ICD-9-CM code(s) to supplement information on PEC prevalence [6]. Only PEC with a study prevalence equal to or $>1\%$ were used in the model development effort.

2.3. Study outcomes

The primary outcome used to develop the model was mortality following traumatic injury, defined as death during the index trauma hospitalization or within 90-days of discharge. Post-discharge deaths were identified by matching patient identifiers to the national Social Security Death Master File, the San Diego County Office of Vital Records and Statistics mortality data, and the California Vital Records index [29]. Follow-up time was calculated from dates of admission to death. Unmatched patients were statistically censored at a time equal to their hospital length of stay plus 90 days. Censoring is performed when a value is only partially known. In this study, we applied it in a traditional sense to unmatched patients assumed to be survivors at a time equal to 90 days after the date of discharge. In-hospital mortality alone was used as a secondary outcome to evaluate the applicability of the model at centers without post-discharge survival status.

2.4. Statistical analysis

Data were managed and analyzed using Stata/MP v.12.1 (Stata-Corp LLC, College Station, TX) and the R Statistical Software version 3.1.3 (R Foundation, Vienna, Austria). The primary cohort was partitioned into two subsets: 3620 patients in a model development subset (80.0%) and 906 in a model test subset (20.0%). Chi-square tests were used to evaluate differences in PEC prevalence by data subset. Correlation among PEC was evaluated using tetrachoric cor-

relation coefficients (ρ) for binary data [30]. ρ values >0.5 or less than -0.5 were considered to be strongly correlated.

Cox proportional hazards regression was used to evaluate the relationship between covariates and mortality. Beta estimates, hazard ratios (HR), and 95% confidence intervals were calculated to evaluate the magnitude of the relationship between each PEC and mortality. To develop the prognostic index based on PEC, the best predictors of mortality were selected using a modified k-fold cross-validation strategy ($k = 4$) across three-stages (Appendix A, Table A2) [31,32]. In brief, candidate PEC were evaluated in univariate and multivariate fashion over three stages and removed if $p > 0.100$. All PEC with a p -value <0.100 and ≥ 0.050 were evaluated using Akaike Information Criterion values and likelihood ratio tests to determine whether their exclusion affected model fitness [33]. The resultant prognostic index from the final model was converted to a point-based system [34]. The total risk score ("PEC Risk Score") was sum of points for PEC present in the final model.

Performance was assessed using time-dependent concordance statistics (c-statistic) calculated at conventional times following admission [35,36]. For each c-statistic, 95% confidence intervals were generated via bootstrapping (100 replicates). Differences in performance between models were identified whereby a 95% confidence interval of one model excluded the c-statistic of another model.

Performance was first evaluated using mortality after traumatic injury and with Cox regression. Second, performance was evaluated for in-hospital mortality using Fine and Gray competing risks modeling, with discharge to a care facility as the competing event. A care facility was defined as: skilled nursing facility, hospice care, acute care facility, rehabilitation center, and behavioral health unit [6]. Calibration plots were developed at three times after admission: 14 days, 90 days, and 120 days (Appendix B, Fig. B1) [31,37].

To assess the practical ability of the PEC Risk Score, c-statistics were calculated for three leading injury-based metrics and two other comorbidity-based metrics. The TMPM probability of death, the TRISS survival probability, and the RTS were evaluated as injury-based metrics. Along with the newly developed PEC Risk Score, the 17-item Charlson Comorbidity Index [38] based on weighted comorbidities by Quan *et al* [39] and a 28-item point-based Elixhauser Comorbidity Score [40] adaptation by van Walraven *et al* [41] were considered comorbidity-based metrics. Using the test set, each of the six metrics were evaluated in head-to-head fashion to evaluate contrasts in singular metric performance. Cumulative in-hospital mortality at 4 weeks (672 h) after admission (capturing $>95\%$ of all in-hospital deaths) in the external test set was used to evaluate combinations of injury- and comorbidity-based metrics to assess the validity of composite models in a general adult trauma population.

3. Results

3.1. Data subsets

Between the development and test subsets, there were no significant differences in the primary outcome of in-hospital death or 90-day post-discharge death (Table 1). Similarly, prevalence for all PEC did not differ between data subsets. Compared to the development subset, patients in the external test set were younger, less injured, experienced shorter hospital length of stay and lower in-hospital mortality, and were less likely to be discharged to a care facility. Of the 27 candidate PEC with prevalence $>1\%$, prevalence was lower for 19 PEC and higher for two PEC in the external test set compared to the development set.

3.2. Model development

The model development procedure identified 12 PEC (Table 2). These included congestive heart failure, myocardial infarction, warfarin therapy, hemophilia, pre-existing anemia, Alzheimer's disease, chronic dementia, cerebrovascular accident/stroke, chronic drug abuse, liver dysfunction, cancers, and renal dysfunction. Two variables had p -values over 0.05: warfarin therapy and liver dys-

Table 1
Study cohort characteristics and PEC prevalence by data subset.

	Development set	Test set	<i>p</i>	External test set	<i>p</i> *
Characteristics					
Sample size	3620	906		2284	
Age in years, mean (SD)	73.8 (11.9)	74.1 (11.6)	0.529	50.8 (22.8)	<0.001
Male sex, n (%)	1922 (53.1)	454 (50.1)	0.108	1461 (65.8)	<0.001
Injury Severity Score, median (IQR)	6 (3–13)	6 (3–13)	0.592	5 (2–9)	<0.001
Discharge to any care facility, n (%)	781 (21.6)	192 (21.2)	0.834	235 (9.1)	<0.001
Hospital length of stay in hours, median (IQR)	50 (24–98)	51 (24–98)	0.942	30 (16–73)	<0.001
Outcomes					
In-hospital death, n (%)	88 (2.4)	25 (2.8)	0.571	32 (1.4)	0.007
Hours to in-hospital death, median (IQR)	98 (53–296)	73 (35–155)	0.128	81 (53–174)	0.303
90-day post-discharge death, n (%)	254 (7.0)	57 (6.3)	0.440	–	–
Days to post-discharge death, median (IQR)	28 (11–56)	33 (8–52)	0.856	–	–
Condition prevalence					
	%	%		%	
Hypertension	61.6	61.5	0.970	34.2	<0.001
Coronary artery disease	25.9	26.3	0.839	9.7	<0.001
Type 2 diabetes	25.7	25.6	0.945	13.9	<0.001
Chronic drug abuse	21.3	18.4	0.055	39.2	<0.001
Warfarin therapy	20.6	19.7	0.521	10.0	<0.001
History of psychiatric disorders	20.2	19.0	0.426	18.2	0.066
Chronic alcohol abuse	13.7	13.0	0.609	25.9	<0.001
Congestive heart failure	13.5	12.8	0.563	6.0	<0.001
Renal dysfunction	13.1	12.7	0.732	7.0	<0.001
Cerebrovascular accident/stroke	11.4	11.7	0.806	6.0	<0.001
Chronic obstructive pulmonary disease	10.1	9.3	0.465	5.1	<0.001
Pre-existing anemia	10.0	8.8	0.300	7.4	0.001
Chronic dementia	9.8	10.0	0.830	7.2	0.001
Myocardial infarction	8.1	8.7	0.521	2.7	<0.001
History of cardiac surgery	7.2	7.8	0.499	4.0	<0.001
Seizures	5.1	4.8	0.654	4.8	0.623
Alzheimer's disease	4.5	4.9	0.622	1.4	<0.001
Coagulopathy	4.1	4.8	0.378	1.9	<0.001
Asthma	4.0	3.5	0.511	4.8	0.158
Type 1 diabetes	3.9	3.8	0.843	1.2	<0.001
History of cancer	3.6	3.2	0.595	1.5	<0.001
Liver dysfunction (including cirrhosis)	3.4	2.9	0.403	2.6	0.067
Hemophilia	2.8	2.2	0.310	2.7	0.797
Obesity	2.7	3.0	0.654	2.8	0.924
Rheumatoid arthritis	2.1	2.7	0.341	1.2	0.011
Parkinson's disease	1.9	2.0	0.788	1.0	0.014
Dialysis (excluding transplant patients)	1.6	1.1	0.320	0.6	0.001

function. Because subsequent models withholding these two variables produced AIC values and significant likelihood ratio tests indicating worse fit, they were retained. The prognostic index was calculated as follows:

$$\begin{aligned}
 \text{Risk} = & 0.6132615 \text{ (Congestive Heart Failure)} \\
 & + 0.4452354 \text{ (Myocardial Infarction)} \\
 & + 0.2167003 \text{ (Warfarin Therapy)} \\
 & + 0.5648907 \text{ (Hemophilia)} \\
 & + 0.2932986 \text{ (Pre – existing Anemia)} \\
 & + 0.4769274 \text{ (Alzheimer's Disease)} \\
 & + 0.5770123 \text{ (Chronic Dementia)} \\
 & + 0.3480417 \text{ (Cerebrovascular Accident/Stroke)} \\
 & + -0.623796 \text{ (Chronic Drug Abuse)} \\
 & + 0.4672339 \text{ (Liver Dysfunction)} + 1.474584 \text{ (Cancers)} \\
 & + 0.6964046 \text{ (Renal Dysfunction)}
 \end{aligned}$$

Cancers conferred the most amount of risk, while chronic drug abuse was deemed protective. Conversion of the beta estimates for all PEC to a point-based system was performed using the calculated estimate for warfarin therapy as the common standardization value (beta = 0.2167003).

Median PEC point scores did not differ between the test and development subsets (Fig. 1). However, maximum values varied slightly (19 in the development subset, 17 in the test subset, and 19 in the external test set). Although development and test subset

scores were distributed similarly, a score of –3 corresponding to chronic drug abuse was evident to a much greater extent in the external test set.

3.3. Correlation between PEC

Correlation coefficients between PEC are shown in Table 3. Among PEC in the final model, high positive correlation was identified between liver dysfunction and hemophilia (rho = 0.58), Alzheimer's disease and chronic dementia (rho = 0.89). High negative correlation was identified between cancer and hemophilia (rho = –1.00), chronic drug abuse and Alzheimer's disease (rho = –1.00), liver dysfunction and Alzheimer's disease (rho = –1.00), and liver dysfunction and chronic dementia

Table 2
Variables and estimates from the final model in the development set.

Condition name	Beta	HR	95% CI	<i>p</i> -value	Points
Congestive heart failure	0.6132615	1.85	1.44–2.37	<0.001	+3
Myocardial infarction	0.4452354	1.56	1.14–2.13	0.005	+2
Warfarin therapy	0.2167003	1.24	0.97–1.58	0.081	+1
Hemophilia	0.5648907	1.76	1.17–2.65	0.007	+3
Pre-existing anemia	0.2932986	1.34	1.01–1.78	0.043	+1
Alzheimer's disease	0.4769274	1.61	1.03–2.53	0.038	+2
Chronic dementia	0.5770123	1.78	1.27–2.50	0.001	+3
Cerebrovascular accident/stroke	0.3480417	1.42	1.07–1.87	0.015	+2
Chronic drug abuse	–0.623796	0.54	0.34–0.78	0.001	–3
Liver dysfunction	0.4672339	1.60	0.98–2.59	0.058	+2
Cancer	1.474584	4.37	3.19–5.99	<0.001	+7
Renal dysfunction	0.6964046	2.01	1.56–2.58	<0.001	+3

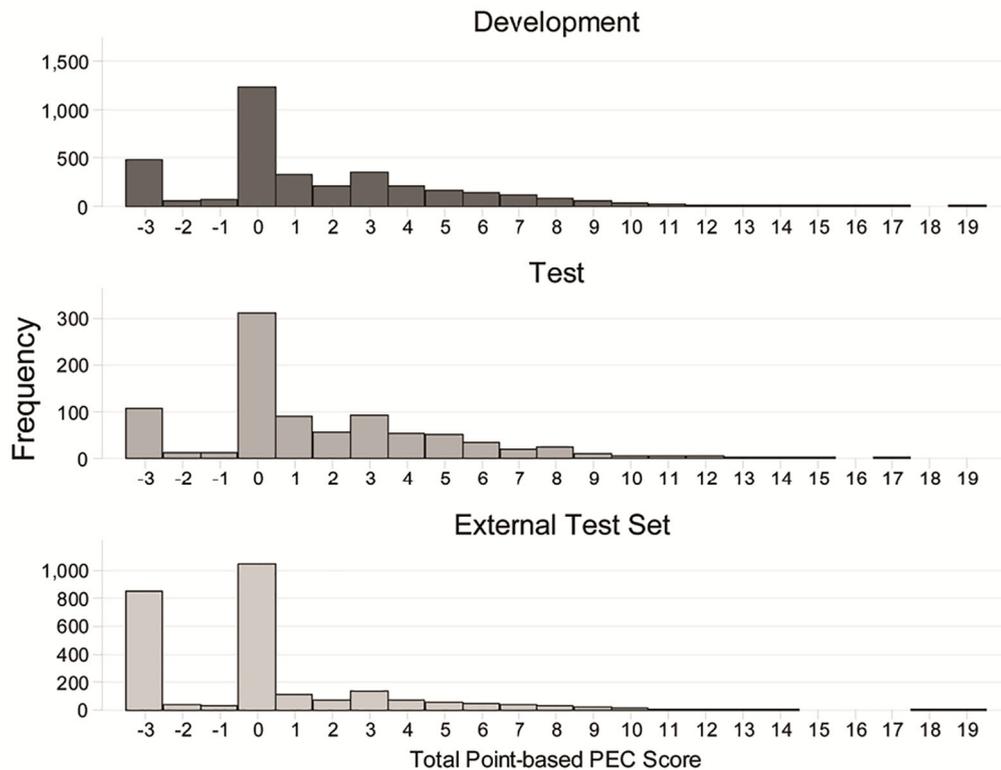


Fig. 1. Histogram of PEC Risk Score totals by data subset.

($\rho = -1.00$). Among all conditions used for modeling, high positive correlations were found between history of cardiac surgery and coronary artery disease ($\rho = 0.75$), coronary artery disease and congestive heart failure ($\rho = 0.55$), coronary artery disease and myocardial infarction ($\rho = 0.58$), history of psychiatric disorders and Alzheimer's disease ($\rho = 0.70$), history of psychiatric disorders and chronic dementia ($\rho = 0.80$), type 1 diabetes and type 2 diabetes ($\rho = 0.67$), and renal dysfunction and non-transplant dialysis ($\rho = 1.00$).

3.4. Evaluation of model performance

Compared to all other metrics, testing of the new PEC Risk Score yielded the highest c-statistics at all times from admission (Table 4). The PEC Risk Score was significantly superior to the Charlson Index at all times evaluated and to the Elixhauser score for both 90-day and 120-day mortality. Although the PEC Risk Score performed similarly to the TMPM, TRISS, and RTS metrics at 7 days from admission, it was statistically superior at predicting cumulative mortality at all times thereafter. For in-hospital mortality, the PEC-Risk Score was the only metric that showed any appreciable discrimination over a 50% null value. After the first 24 h from admission, the PEC Risk Score consistently predicted mortality at all subsequent times.

The addition of a comorbidity-based metric significantly improved the predictive performance compared to any injury-based metric alone (Table 5). Although the baseline performance of each injury metric ranged from very poor (TMPM c-statistic = 50.8) to moderate (TRISS c-statistic = 78.8), inclusion of any of the three comorbidity-based metrics resulted in a statistically significant improvement in the composite model's ability to correctly classify survival among trauma patients. In comparing comorbidity-based metrics, the PEC Risk Score and Charlson index resulted in similar improvements to performance after being added to any of the three injury-based models, and both consistently outperformed the Elixhauser metric.

4. Discussion

We developed and tested a brief PEC Risk Score to predict mortality after injury in patients older than 55 years with minor injury. Testing of our metric showed that it out-performed three widely used injury-based metrics, including TRISS, TMPM and RTS. Our model performed well in comparison with two other comorbidity-based metrics, the 28-item Elixhauser score and the 17-item Charlson Index. Based on only 12 items, our PEC Risk Score offers the ability to effectively assess the risk of mortality after minor traumatic injury in a more efficient manner.

Prevalence of PEC has increased significantly over time and has been considered a force behind poor outcomes in older patients [42]. Large-scale studies performed using national samples have shown significant associations between PEC and mortality in older trauma patients [43–45], but there is significant variation in the methods used for their measurement. Wardle *et al* [43], using the UK Trauma, Audit, and Research Network, McGwin *et al* [44], using the US National Trauma Databank (NTDB), and Shoko *et al* [45], using the Japan Trauma Databank (JTDB), evaluated PEC with in-hospital mortality, but focused on counting conditions to measure the burden of disease and thus assumed equal weight for each. Our study sought to address this gap in the literature by calculating a weight for each of the most relevant PEC.

The present study provides a direct assessment of PEC specific to trauma patients, a measure by which studies of existing prognostic metrics have fallen short. In one study, many conditions incorporated in the Elixhauser metric were found not statistically significantly associated with in-hospital mortality after trauma, bringing into question its validity for trauma patients [6]. In another study, Thompson *et al* [23] attempted to calculate weights for specific PEC on mortality after trauma. However, their model was developed using a large-scale administrative dataset meant to evaluate trauma care value. As such, it lacked age- or injury-based sample restrictions necessary to control for confounding and subsequently did not compare favorably to other metrics.

Table 3
Tetrachoric correlation coefficients among candidate PEC.

#	Chronic Condition	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28
1	History of cardiac disease	1.00																											
2	Coronary artery disease	0.76	1.00																										
3	Congestive heart failure	0.30	0.44	1.00																									
4	Myocardial infarction	0.32	0.65	0.30	1.00																								
5	Hypertension	0.18	0.28	0.21	0.12	1.00																							
6	History of psychiatric disorders	0.06	0.03	0.13	-0.07	0.04	1.00																						
7	Coagulopathy	0.19	0.18	0.17	0.02	0.16	0.09	1.00																					
8	Warfarin Therapy	0.23	0.26	0.34	0.02	0.24	-0.03	0.13	1.00																				
9	Hemophilia	0.14	0.11	0.16	0.13	-0.02	0.10	0.18	-0.04	1.00																			
10	Pre-existing Anemia	-0.02	0.16	0.20	0.09	0.06	0.09	0.20	0.01	0.38	1.00																		
11	Alzheimer's Disease	0.11	0.09	0.09	0.01	0.14	0.71	0.07	0.00	0.05	0.04	1.00																	
12	Seizures	-0.07	0.02	0.04	0.02	0.01	0.23	0.02	0.00	0.22	0.01	0.04	1.00																
13	Dementia	0.09	0.10	0.18	-0.02	0.17	0.83	0.11	0.08	-0.04	0.13	0.88	0.03	1.00															
14	Parkinson's Disease	0.04	0.17	0.07	0.02	0.01	0.20	0.15	0.07	-0.11	0.15	0.27	-0.03	0.30	1.00														
15	CVA/stroke	0.17	0.20	0.10	0.22	0.25	0.08	0.18	0.27	0.11	0.09	0.05	0.10	0.15	0.05	1.00													
16	Chronic drug Abuse	-0.20	-0.18	-0.28	-0.15	-0.22	-0.01	-0.13	-0.22	-0.04	-0.12	-0.34	0.19	-0.37	-0.33	-0.12	1.00												
17	Chronic alcohol abuse	-0.29	-0.22	-0.21	-0.12	-0.20	-0.06	-0.10	-0.22	0.23	-0.01	-0.40	0.22	-0.36	-1.00	-0.15	0.76	1.00											
18	Asthma	0.05	0.08	0.06	-0.02	0.15	0.02	0.13	0.04	0.04	-0.19	-0.22	-0.04	-0.03	0.02	-0.09	-0.09	-0.12	1.00										
19	COPD	-0.01	0.22	0.35	0.16	0.05	0.19	0.05	0.10	-0.03	0.12	-0.06	0.20	-0.01	0.07	0.08	0.08	0.03	0.26	1.00									
20	Chronic pulmonary condition	-0.04	0.01	0.15	0.00	-0.05	-0.01	0.10	0.03	-0.14	0.06	-0.06	0.12	-0.12	-0.17	-0.13	0.06	-0.04	0.18	0.52	1.00								
21	Type 1 diabetes	0.27	0.21	0.09	0.10	0.16	0.02	0.15	0.08	0.13	0.09	-0.01	0.12	0.01	-0.04	0.15	-0.16	-0.15	0.09	0.07	-0.11	1.00							
22	Type 2 diabetes	0.24	0.22	0.13	0.12	0.30	0.00	0.08	0.03	0.00	0.14	-0.01	0.06	0.07	-0.07	0.09	-0.15	-0.19	0.09	0.04	0.02	0.59	1.00						
23	Liver dysfunction	-0.12	-0.14	0.09	0.01	-0.08	0.03	0.26	-0.16	0.49	0.29	-0.28	0.23	-0.28	-0.14	-0.11	0.18	0.39	0.08	0.10	0.08	0.13	0.10	1.00					
24	Cancers	0.07	-0.03	0.00	0.03	0.08	-0.08	0.17	0.09	0.09	0.31	-0.09	-0.11	-0.01	-0.04	-0.09	-0.05	-0.10	0.06	0.21	0.22	0.11	-0.01	0.10	1.00				
25	Rheumatoid arthritis	-0.21	-0.02	0.05	-0.03	0.09	-0.05	0.01	-0.01	-0.04	0.11	0.09	0.07	0.06	-1.00	0.02	-0.07	-0.33	0.08	0.09	0.19	0.09	0.06	-0.07	-0.08	1.00			
26	Obesity	-0.02	0.09	0.04	0.09	0.21	0.01	-0.03	0.09	0.00	0.12	-0.09	0.12	-0.20	-1.00	-0.16	0.00	-0.08	0.43	0.12	0.04	0.25	0.24	0.15	-0.05	0.04	1.00		
27	Renal dysfunction	0.24	0.28	0.38	0.27	0.06	0.03	0.11	0.05	0.37	0.40	-0.01	-0.07	0.10	0.00	0.18	-0.28	-0.23	-0.03	0.15	-0.03	0.34	0.27	0.11	0.13	-0.03	0.13	1.00	
28	Non-transplant dialysis	0.27	0.27	0.18	0.15	0.00	-0.01	0.00	-0.05	0.07	0.07	-0.01	-0.03	0.06	0.02	0.06	-0.26	-0.32	0.02	0.10	-0.10	0.47	0.30	-0.07	0.03	-1.00	-0.05	1.00	1.00

Table 4
Concordance statistics by model in the test set at various times from admission.

	Mortality after traumatic injury				
	7 days	14 days	30 days	90 days	120 days
Deaths (%)	24 (29.3)	35 (42.7)	49 (59.8)	79 (96.3)	81 (98.8)
PEC risk score	77.7 (69.6–85.8)	79.4 (73.4–85.3)	79.3 (73.8–84.7)	81.1 (76.9–85.3)	79.7 (76.7–83.7)
Charlson	68.7 (58.9–78.5)	68.0 (59.6–76.4)	66.6 (59.3–74.0)	72.1 (66.3–77.9)	71.3 (65.7–76.8)
Elixhauser	74.1 (64.9–83.4)	74.8 (67.2–82.3)	73.9 (67.2–80.5)	75.9 (70.5–81.3)	75.0 (69.8–80.1)
TMPM	65.0 (52.6–77.4)	62.6 (52.1–73.1)	63.7 (54.4–73.0)	61.8 (54.9–68.8)	61.8 (55.1–68.5)
TRISS	73.8 (62.0–85.5)	72.0 (62.0–82.0)	73.6 (65.6–81.5)	66.3 (59.4–73.2)	34.5 (18.9–50.0)
RTS	74.3 (64.2–84.3)	69.6 (61.3–77.9)	66.7 (59.9–73.5)	60.6 (55.5–65.7)	50.3 (38.4–62.2)
	In-hospital mortality				
	24 h	72 h	168 h (1 week)	336 h (2 weeks)	672 h (4 weeks)
Deaths (%)	5 (20.0)	12 (48.0)	19 (76.0)	22 (88.0)	24 (96.0)
PEC risk score	58.0 (30.5–85.5)	74.4 (60.5–88.3)	69.5 (59.1–80.0)	71.6 (59.7–83.4)	75.4 (58.7–92.1)
Charlson	69.9 (48.7–91.1)	63.2 (49.3–77.0)	58.5 (44.1–72.9)	66.1 (52.3–79.9)	59.4 (41.5–77.4)
Elixhauser	68.5 (52.3–84.7)	58.9 (44.9–73.0)	59.3 (43.0–75.6)	66.4 (51.0–81.7)	65.2 (47.1–83.2)
TMPM	48.2 (21.7–74.7)	59.7 (40.4–79.0)	50.4 (33.3–67.4)	40.7 (24.0–57.5)	44.4 (26.8–62.0)
TRISS	63.0 (36.2–89.8)	65.4 (46.5–84.4)	58.2 (44.0–72.4)	43.8 (27.5–60.0)	42.7 (23.4–62.1)
RTS	77.9 (56.0–99.8)	72.2 (57.3–87.2)	68.1 (55.3–80.8)	62.1 (49.4–74.7)	52.4 (37.9–66.9)

Table 5
Concordance statistics by model combination in the external test set for in-hospital mortality.

Injury metric	Comorbidity metric added			
	None	PEC risk score	Charlson	Elixhauser
TMPM	50.8 (43.8–57.8)	84.6 (79.4–89.8)	82.4 (81.3–83.5)	83.0 (82.0–84.0)
TRISS	78.8 (76.3–81.3)	92.6 (90.1–95.1)	93.4 (91.9–94.4)	88.6 (85.8–91.7)
RTS	63.8 (62.0–65.6)	91.8 (89.1–94.5)	91.8 (89.1–94.5)	87.1 (83.2–91.0)

Other efforts to revise existing trauma mortality metrics by incorporating either the Charlson or Elixhauser systems have varied in success; however, all have neglected to weigh PEC for trauma patients [17–22]. This study further supports the work of researchers who contend that, for the majority of older trauma patients who tend not to have severe injuries, PEC is a stronger predictor of mortality risk factor than injury [2–5,11,12].

Prior research has called for the incorporation of PEC in risk classification to improve accuracy. Using the Trauma Quality Improvement Project database, Calland *et al* [46] identified significant differences in the effects of trauma risk factors by age and recommended that improvements to existing risk adjustment models may be achieved through the inclusion of comorbidities. Bergeron *et al* [20] evaluated the TRISS calculation and identified that the predictive performance of TRISS was improved through the inclusion of a simple binary variable to denote the presence of comorbidities. Our study took this a step further: The PEC Risk Score is a weighted score of specific comorbidities shown to affect survival specific to trauma patients. Despite its development and testing with an older and minimally injured population, inclusion of the PEC Risk Score to any of the three injury-based metrics resulted in improved predictive performance in a general trauma population. This reinforces the recommendation that a measure of comorbidity burden should be included in trauma risk prediction models.

Given the PEC Risk Score is the most parsimonious of the three comorbidity-based models evaluated with no sacrifice to performance, we recommend its use in future research.

Although the PEC used in our model were defined by the hospital trauma registry, many overlapped with conditions found in the other comorbidity-based metrics. Four of these PEC conferred an increase in mortality risk consistent with that found in the study by Thompson *et al* [23]. Surprisingly, chronic drug abuse showed a protective effect for mortality. This association was also seen in the study by van Walraven *et al* [41] and was incorporated into their version of the Elixhauser metric. This was likely due to patients with chronic drug abuse being, on average, 10.1 years younger than those without chronic drug abuse (65.9 vs. 76.0 years), and that chronic drug abuse was largely the only condition present in a majority of patients who were also survivors. Hemophilia, a condition not found in other PEC metrics, posed a unique risk to trauma patients in our study, likely because of the risk of hemorrhage.

In our model, the greatest amount of risk was associated with cancer and renal dysfunction which equates itself with patients who may require end of life care. The remaining conditions of liver dysfunction, myocardial infarction, CVA/stroke, congestive heart failure, warfarin therapy, pre-existing anemia, Alzheimer's disease, and chronic dementia all coincide with advanced age, significant cardiovascular disease, and a diminished physiologic reserve. Similar associations were demonstrated in the NTDB, JTDB, and TARN studies [43–45]. Cardiac conditions, liver dysfunction, and COPD were strong risk factors consistent with studies done from the NTDB and JTDB [44,45]. Stroke and hematologic conditions, which included anticoagulation therapy, hemophilia, and anemia were positively associated with mortality in the JTDB study [45]. Similarly, dementia and cancer were strong risk factors identified in both the TARN and JTDB studies [4,45].

The assumption of uniformity of risk over time is a major weakness affecting predictive metrics in trauma [47]. We assessed variations in mortality risk calculated by each metric at various times from admission. We found that the comorbidity-based metrics and the injury-based metrics had differential predictive performance, with the latter declining with time. The classification of trauma mortality risk may be a function of changes in patient health profiles such that the severity of injury overwhelmingly impacts mortality risk early and is replaced by PEC with additional survival time. Therefore, for predicting mortality in older trauma populations who tend to expire later after admission, standard injury-based metrics are inadequate.

Our PEC Risk Score was developed using an outcome which combined in-hospital death and death within 90 days of discharge. Incorporation of deaths during the 90-day post-discharge period sought to address a significant bias associated with misclassifying survivorship due to a loss-to-follow-up such as discharge [10,48,49], and was selected based on previous work which indicated that trauma influenced mortality up to 90 days after discharge [12,29]. Nearly three times as many patients died within 90 days of discharge as did in-hospital. These patients would traditionally be censored in studies that do not evaluate mortality after discharge, thereby minimizing the role of their prevalent PEC. If researchers were to assume homogeneity of mortality risk for all discharged patients, estimates of risk may be biased in favor of the characteristics of patients with post-discharge placement issues and other factors temporally proximal to the time of admission. This bias ignores the relevance of the entire spectrum of patient health, focusing only on that of injury and other hospital-based measures [50].

Owing to the low mortality rate, we used a conservative variable selection method to prevent model overfitting. Many PEC were excluded early in the multivariable model development process despite demonstrating some risk but were omitted because of redundancy. For example, coronary artery disease showed high correlation with both congestive heart failure and myocardial infarction, but failed to be statistically significant to mortality during the latter stages of model development. Although coronary artery disease may be a risk factor for death, its explanatory power was sufficiently captured by the two other correlated conditions. Future

work on model tuning may yield improvements in prediction of our PEC Risk Score.

This study has several limitations pertaining to model validation and patient selection. First, model development and evaluation was performed devoid of a marker of frailty which is a growing topic in the trauma literature. Because of the potential for correlation between the domains of frailty and comorbidity, the performance of our metric may vary by frailty status. The external test set did not have post-discharge mortality information and competing risks regression was employed to analyze in-hospital mortality in its place. At the outset of the present study, post-discharge data sources with sufficient follow-up time were not available for the 2013 cohort. Although an assessment of true external validity would have been performed using the same outcome and in a more diverse sample, our study demonstrates the applicability of competing risks regression and our PEC Risk Score for trauma centers lacking post-discharge mortality data. Our attempts to validate the PEC Risk Score in the Trauma Quality Improvement Program and NTDB were mixed (data not shown). These data sources aggregate PEC into broad groupings and demonstrated significantly different PEC prevalence compared with that of our study population. Our PEC Risk Score was developed in a subpopulation of older blunt-injured trauma patients with high injury-based survival probability which may affect its generalizability to more injured populations. However, the grand majority (> 98%) of our older trauma patients had low injury severity, and represented a group in which mortality risk has notoriously been difficult to assess [51,52]. Furthermore, as the majority of older trauma patients did not experience severe injuries but still died, the study population exemplified a large group of patients for whom mortality risk is not adequately classified using existing standards. Despite these limitations, we believe

our use of less severely injured older patients was justified not only to reduce confounding due to severe injury (which occurred in a small minority of the population), but because this group stands to gain the most from an applicable measure of PEC burden.

5. Conclusions

In conclusion, our 12-item PEC Risk Score performed well compared to existing prognostic metrics, offering a novel tool to calculate PEC burden and predict mortality in older trauma patients. Future work aimed at validating the PEC Risk Score in larger samples that include multicenter trauma populations is warranted and will expand the evidence base that trauma researchers and clinicians can apply. Moreover, given the increasing volume of older trauma patients, most of whom have PEC, performance assessment of trauma centers should account for the effect of PEC on outcome.

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Appendix A. PEC definitions and model development

A.1. Candidate conditions

A total of 45 PEC were identified for analysis (Table A1). Of these, 18 PEC were excluded for low prevalence: all gastric disorders (peptic ulcer disease, gastric or esophageal varices, pancreatitis, inflammatory bowel disease), all immunosuppression conditions (HIV/AIDS, routine steroid therapy, transplants, active chemotherapy), pulmonary heart disease, congenital cardiac disease, attention deficit disorder, mental retardation, spinal cord injury, multiple sclerosis, chronic demyelinating disease, organic brain syndrome, history of pulmonary condition with ongoing treatment, and lupus. After exclusions, 27 PEC were retained as candidate variables for model development.

A.2. Model development

Data were randomly partitioned into two sets: 3620 patients in a development set for model development (80.0%), and 906 in a test set for model testing (20.0%). The development set was further partitioned into quarters for development of a PEC-based mortality risk model. To develop a prognostic model based on PEC, the Cox proportional hazards models were used on the primary outcome of mortality after traumatic injury. Covariate selection was performed in three stages (Table A2). Stage 1 iteratively used three of the four subsets of the development set to evaluate each PEC in univariate fashion. Conditions were modeled a total of four times, omitting one subset in each iteration with replacement. Selection of PEC for the second stage of development was based on a p -value <0.100 in at least two of four iterations. Stage 2 introduced all of the eligible PEC into a combined full model and featured the sequential removal of the least significant PEC. For this stage, each sequence of the model was analyzed in four iterations in the same leave-one-set-out fashion as the previous stage. A PEC was selected for removal from the model based having the highest average p -value across these iterations. Variables were retained for stage 3 evaluation if they achieved a p -value <0.100 in at least one of four iterations. For the third and final stage, the remaining candidate PEC were combined and modeled in the entire development set. Variables were excluded based on a p -value >0.100. For the final variable subset, Akaike Information Criterion (AIC) values and likelihood ratio tests were used to evaluate changes in model fit after removal of variables with p -values >0.05. If exclusion of a variable resulted in a worse-fit model, the variable was retained. The initial prognostic index for mortality after traumatic injury was calculated using the resultant beta coefficients from the final model.

Among all the candidate conditions used for modeling, only those related at the p < 0.100 level were retained for multivariable modeling. Because of the relatively low event rate, caution was required when selecting variables for inclusion to prevent overfitting. As such, conditions that experienced high correlation with that of a selected variable may still be valid risk factors that were omitted due to redundancy. Specifically, coronary artery disease showed high correlation with both congestive heart failure and myocardial infarction, but failed to be statistically significant to mortality during the second stage of model development. It should be noted that initial rounds of multivariable model development showed history of cardiac surgery, coronary artery disease, congestive heart failure, and myocardial infarction as being significant during stage 1 but lost significance in early iterations of stage 2. Only one covariate was removed at a time due to fear of multicollinearity preventing proper estimation of the covariates and it was not until the very last iteration of stage 2 that coronary artery disease was dropped from the list of candidate variables. In the third stage, chronic alcohol abuse was eventually removed, but generally

was not significantly related to mortality through much of the stage 2 iterations. As correlation was high between chronic drug abuse and chronic alcohol abuse, the explanatory power associated with alcohol abuse is likely to be captured by the drug abuse variable. The same is likely true for non-transplant dialysis which showed a perfect correlation with that of renal dysfunction. Non-transplant dialysis was significant in three of four stage 1 iterations and was retained long into stage 2.

Table A1
Trauma registry PEC and coding definitions

PEC name	Registry code	ICD-9-CM Code
Cardiac diseases	Prefix = "A"	
History of cardiac surgery	Suffix = "01"	429.4, 997.1, 668.1, 996.61
Coronary artery disease	Suffix = "02"	414.xx, 747.3, 414.8
Congestive heart failure	Suffix = "03"	428
Pulmonary heart disease	Suffix = "04"	415.0, 416.9
Myocardial infarction	Suffix = "05"	412, 411.81, 429.7, 410.x, 414.2
Hypertension	Suffix = "06"	401, 402, 404, 997.91, 459.30, 459.3
Congenital cardiac disease	Suffix = "07"	427.9, 746.85–746.89
Diabetes mellitus	Prefix = "B"	
Insulin dependent (type 1)	Suffix = "01"	250.01, 250.03, 250.11, 250.13, 250.21, 250.23, 250.31, 250.33, 250.41, 250.43, 250.51, 250.53, 250.61, 250.63, 250.71, 250.73, 250.81, 250.83, 250.91, 250.93
Non-insulin dependent (type 2)	Suffix = "02"	249.x, 250.00, 250.02, 250.10, 250.12, 250.20, 250.22, 250.30, 250.32, 250.40, 250.42, 250.50, 250.52, 250.60, 250.62, 250.70, 250.72, 250.80, 250.82, 250.90, 250.92, 648.0
Gastrointestinal conditions	Prefix = "C"	
Peptic ulcer disease	Suffix = "01"	531.7, 531.9, 532.7, 532.9, 533.7, 533.9, 534.7, 534.9
Gastric/esophageal varices	Suffix = "02"	456.0, 456.1, 437.89
Pancreatitis	Suffix = "03"	577.0, 577.1
Irritable bowel disease	Suffix = "04"	564.1
Hematologic disorders	Prefix = "D"	
Coagulopathy	Suffix = "01"	288–289, 283.x, 286.7
Warfarin therapy (i.e. coumadin)	Suffix = "02"	V58.61, V58.83, 453.40
Hemophilia	Suffix = "03"	286.0–286.6
Pre-existing anemia	Suffix = "04"	280.x–285, 678.x
Psychiatric disorders	Prefix = "E"	
History of psychiatric disorders	Suffix = "00"	293.84, 294.x, 295, 296
Attention deficit disorders	Suffix = "01"	314.x
Mental retardation	Suffix = "02"	315.x, 317–319
Immunosuppression	Prefix = "F"	
HIV/AIDS	Suffix = "01"	042
Routine steroid therapy	Suffix = "02"	V58.65
Transplants	Suffix = "03"	996.81, 279.3, 279.8, V87.46
Active chemotherapy	Suffix = "04"	V58.1x, 285.3
Liver diseases, including cirrhosis and bilirubin >2 mg%	Prefix = "G"	070, 456.0, 456.1, 456.2, 570, 571, 572.2, 572.3, 572.4, 572.8, 573.3, 573.4, 573.8, 573.9, V42.7, 200–203.0, 238.6
Cancers, includes undergoing therapy, lymphoma, metastasis, or old malignancy	Prefix = "H"	200–203.0, 238.6, 196–199, 140–195
Autoimmune disorders	Prefix = "I"	
Rheumatoid arthritis	Suffix = "01"	714.0
Systemic lupus erythematosus	Suffix = "02"	373.34, 695.4, 710.0
Neurologic	Prefix = "J"	
Spinal cord injury	Suffix = "01"	952.xx
Multiple sclerosis	Suffix = "02"	340
Alzheimer's disease	Suffix = "03"	331.0
Seizures	Suffix = "04"	345.x
Chronic demyelinating disease	Suffix = "05"	341.x
Chronic dementia	Suffix = "06"	290.x, 294.1x–294.2x
Organic brain syndrome	Suffix = "07"	294.0
Parkinson's disease	Suffix = "08"	332.x
Cerebrovascular accident (stroke)	Suffix = "09"	433.x, 434.x, 436.x, V12.54
Obesity	Prefix = "K"	278.0
Pulmonary disease	Prefix = "L"	
Prior history with active treatment	Suffix = "01"	V58.65
Asthma	Suffix = "02"	493.x
Chronic obstructive pulmonary disease	Suffix = "03"	490–492.x, 466.0, 496
Renal disorders	Prefix = "M"	
Chronic and acute kidney disorders, includes serum creatinine >2 mg%	Suffix = "01"	403.01, 403.11, 403.91, 404.02, 404.03, 404.12, 404.13, 404.92, 404.93, 585, 586, 588.0, V42.0, V45.1, V56, 584.5–9, 593.9, 583.6
Non-transplant dialysis	Suffix = "02"	V45.11, V56, 996.73, 996.56, E879.1, E870.2, E871.2, E872.2, E874.2, 792.5
Substance abuse	Prefix = "N"	
Chronic ongoing drug abuse	Suffix = "01"	292.x, 304.x, 305.x
Chronic ongoing alcohol abuse	Suffix = "02"	291.x, 303.x

ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; PEC, Pre-existing Conditions.

Table A2
Model development stages and significance counts of candidate PEC

PEC name	Stage 1.0	Stage 2.0	Stage 2.1	Stage 2.2	Stage 2.3	Stage 2.4	Stage 2.5	Stage 2.6	Stage 3.1	Stage 3.2	Stage 3.3	Stage 3.4
	Count	<i>p</i>	<i>p</i>	<i>p</i>	<i>p</i>							
History of cardiac surgery	4	0	–									
CAD	4	0	0	0	0	0	0	–				
CHF	4	4	4	4	4	4	4	4				
Myocardial Infarction	4	4	4	4	4	4	4	4				
Hypertension	0	–										
History of psychiatric disorders	4	0	0	0	–							
Coagulopathy	3	0	0	0	0	–						
Warfarin therapy	4	1	1	1	1	1	1	1		0.082	0.077	0.081
Hemophilia	4	3	3	3	3	3	4	3				
Pre-existing anemia	4	2	2	3	2	2	2	2				
Alzheimer's disease	4	2	2	2	2	2	2	2				
Seizures	0	–										
Dementia	4	4	4	4	4	4	4	4				
Parkinson's disease	3	0	0	0	1	1	1	1	0.296	–		
CVA/stroke	4	3	3	3	3	3	3	2				
Chronic drug abuse	4	4	4	4	4	4	4	4				
Chronic alcohol abuse	4	0	0	0	0	0	0	1	0.162	0.152	–	
Asthma	1	–										
COPD	4	1	1	1	1	1	1	1	0.115	0.116	0.124	–
Type 1 diabetes	4	0	0	–								
Type 2 diabetes	0	–										
Liver dysfunction	2	3	3	3	3	3	2	1				0.058
Cancers	4	4	4	4	4	4	4	4				
Rheumatoid arthritis	0	–										
Obesity	0	–										
Renal dysfunction	4	4	4	4	4	4	4	4				
Non-transplant dialysis	3	0	0	0	0	0	–					

CAD, Coronary Artery Disease; CHF, Congestive Heart Failure; CVA, Cerebrovascular Accident; COPD, Chronic Obstructive Pulmonary Disease.

Stage 1: Iterative Univariate relationships evaluated at *p* < 0.100

Stage 2: Iterative Multivariable relationships evaluated at *p* < 0.100

Stage 3: Complete Development Set Multivariable relationships evaluated at *p* < 0.100.

Appendix B. Point assignment and diagnostics

B.1. Point-based risk score

Point assignment for each PEC was based on methods used for the Framingham Risk Score, where weights were derived using beta estimates for a referent variable within a predictive model. In short, beta estimates for all variables included in the final model were divided by the beta estimate from the referent variable. For the present study, the referent variable was selected based on having the beta estimate closest to a null value, thus producing an integer point value of +1 for this PEC. Point values for all other risk factors were rounded to the nearest integer. The total risk score was calculated by summing the points for all PEC contained in the final model.

B.2. Model calibration

Calibration of the PEC Risk Score was assessed at three times from admission (Fig. B1). For each of these times, plots generally followed the diagonal which indicated that models were calibrated for the test data. In the first 14 days from admission, observed survival exceeded predicted estimates for predicted values <90%, but calibration improved with additional follow-up time and as events accumulated. However, a low event rate restricted the calculation of predicted probabilities under 60% despite 120 days of follow-up time.

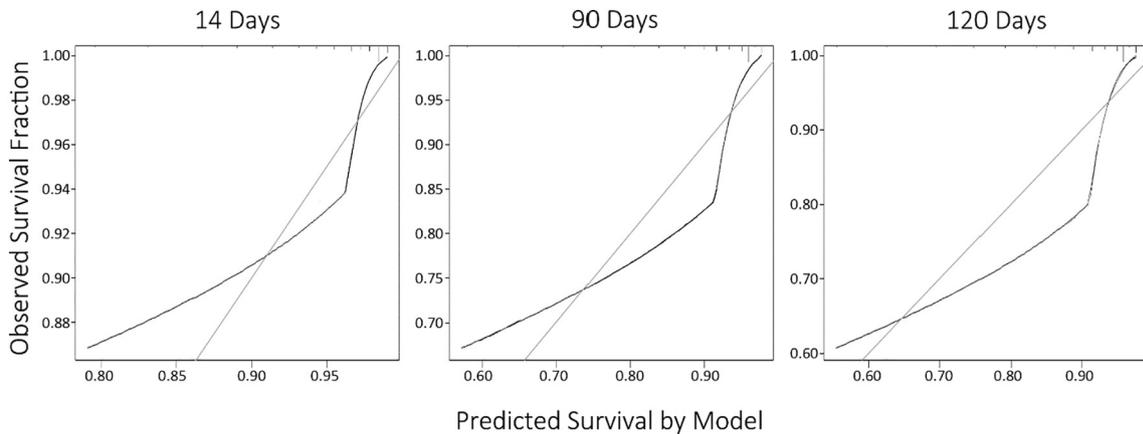


Fig. B1. Calibration plots for mortality after traumatic injury in the test set at three time points from admission.

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