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Validation of the In-Hospital Mortality for Pulmonary Embolism Using Claims Data (IMPACT) Prediction Rule Within an All-Payer Inpatient Administrative Claims Database

Running title: Validation of the IMPACT Rule

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Study concept and design: CGK, CIC, CC, JRS, FWP. Acquisition of data: CIC, CC, JRS. Analysis and interpretation of data: CGK, CIC, CC, JRS, WFP. Drafting of the manuscript: CKG, CIC, FWP. Critical revision of the manuscript for important intellectual content: CIC, CC, JRS, FWP. Administrative, technical, or material support: CIC. CC, JRS. Study supervision: CIC. CGK and CIC had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors read and approved the final manuscript. The authors meet criteria for authorship as recommended by the International Committee of Medical Journal Editors (ICJME) and were fully responsible for all content and editorial decisions, and were involved in all stages of manuscript development.

CONFLICTS OF INTEREST
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ABSTRACT

Objective: To validate the In-hospital Mortality for PulmonAry embolism using Claims daTa (IMPACT) prediction rule, originally developed in a commercial claims database, in a database consisting only of inpatient claims.

Design: Retrospective claims database analysis.

Setting: The 2012 Healthcare Cost and Utilization Project Nationwide Inpatient Sample

Participants: Adult PE admissions were identified by the presence of an appropriate International Classification of Diseases, ninth edition (ICD-9) code either in the primary position or secondary position when accompanied by a primary code for a PE complication. The IMPACT rule, which includes age and 11 comorbidities, was used to estimate patients' probability of in-hospital mortality and classify them as low- or higher-risk (≤1.5% deemed low-risk).

Primary and secondary outcome measures: The rule's sensitivity, specificity, positive and negative predictive values (PPV and NPV) and area under the receiver operating characteristic curve (AUC) statistic for predicting in-hospital mortality with accompanying 95% confidence intervals (CIs).

Results: A total of 34,108 admissions for PE were included; with a 3.4% in-hospital case-fatality rate. IMPACT classified 11,025 (32.3%) patients as low-risk; and low-risk patients had significantly lower in-hospital mortality (odds ratio, 0.17, 95%CI=0.13-0.21), shorter LOSs (-1.2 days, p<0.001) and lower total treatment costs (-$3,074, p<0.001) than patients classified as higher-risk. IMPACT had a sensitivity of 92.4%, 95% confidence interval (CI)=90.7-93.8 and specificity of 33.2%, 95%CI=32.7-33.7 for classifying mortality risk. It had a high NPV (>99%), low PPV (4.6%) and an AUC of 0.74, 95%CI=0.73-0.76.

Conclusion: The IMPACT rule appeared valid when used in this all-payer, inpatient only administrative claims database. Its high sensitivity and NPV suggests the probability of in-hospital death in those classified as low-risk by IMPACT was minimal. IMPACT may be valuable to those wishing to identify PE patients who could safely be treated at home or following an abbreviated hospital admission.

ARTICLE SUMMARY

Strengths and limitations of this study

- Many of the 11 comorbidities of the IMPACT rule were coded for within the claims data using the validated AHRQ 29-comorbidity software/schema.
- Due to the lack of out-of-hospital mortality data in the NIS, we could not evaluate longer-term (30-day) mortality of these patients.
- As with all claims databases, the NIS may contain inaccuracies or omissions in coded diagnoses/procedures, leading to the potential for misclassification bias.
- The 1.5% cut-point for defining low-risk for in-hospital mortality can be considered arbitrary; but was chosen (in the original derivation study) based upon review of AUC analysis and previous clinical prediction rules.

The incidence of pulmonary embolism (PE) in US has increased substantially over the past decade; with incidence estimates surpassing 112 PEs per 100,000 Americans [1]. This increased PE incidence has been attributed to improved diagnostic modalities and is associated with a decreased overall case fatality rate. Some have used these data to suggest there are a substantial fraction of PE patients that could potentially be discharged directly from the emergency department, observational unit or from the hospital following an abbreviated stay [1-3]. However, to do so, would require a method for estimating a PE patients' risk of complications, in particular, early mortality.

Numerous clinical prediction rules for prospectively estimating PE patient's short-term mortality have been developed [4]. The PE Severity Index (PESI) [5], simplified PESI (sPESI) [6] and Hestia [7] scores are among the most sensitive for classifying early mortality risk; and suggest at least one-third of all PE patients could be treated at home or following an abbreviated admission [4]. A common theme of these prediction rules is their use of vital signs and laboratory values in addition to comorbidity status [4]. For this reason, these rules cannot be implemented in most administrative claims databases. In the current era of cost-conscious healthcare, there is a growing need for a benchmarking rule that payers and hospitals can use to assess whether they are providing optimal and efficient acute care for patients presenting with PE.

Coleman and colleagues derived such a benchmarking rule for in-hospital PE mortality using a large, US commercial claims database [8]. This prediction rule, dubbed the In-hospital Mortality for Pulmonary embolism using Claims data (IMPACT), consists of 11 comorbidities identified using in- or outpatient claims data during the 12-months prior to the index PE event (plus age as a continuous variable) and was demonstrated to have a sensitivity and specificity similar to PESI and sPESI [4]. However, because there are many hospital-specific and commercial claims databases which contain only data from

inpatient admissions [9], they contain insufficient claims data to identify relevant comorbidities to populate the above-mentioned rule.

The aim of this study was to determine whether the validity of the IMPACT prediction rule developed in a commercial claims database remained acceptable when utilized in an inpatient only claims database.

METHODS

We utilized the 2012 Agency for Healthcare Research and Quality Healthcare Cost and Utilization Project Nationwide Inpatient Sample (NIS) for this study [10]. The NIS contains data on hospital inpatient stays and covers all patients, including those with Medicare, Medicaid, private insurance and the uninsured. The 2012 inpatient core file contained data on 7,296,968 hospitalizations occurring between January 1, 2012 and December 31, 2012 and was drawn from 4,378 hospitals within 44 states. As only analysis on de-identified data was performed, our study was exempt from institutional review board oversight.

Patients ≥18 years of age with a diagnosis of PE were identified using International Classification of Diseases, ninth edition, Clinical Modification (ICD-9-CM) codes indicating PE as the primary diagnosis (415.11, 415.12, 415.13 and 415.19). To allow for the inclusion of seriously ill patients with PE, we also included admissions with a secondary diagnosis code for PE and a primary code representing one of the following common complication/treatment of PE: respiratory failure (518.81), cardiogenic shock (785.51), cardiac arrest (427.5), secondary pulmonary hypertension (416.8), syncope (780.2), thrombolysis (99.10) and intubation/mechanical ventilation (96.04, 96.05, 96.70-96.72). Admissions with only a secondary diagnosis of PE and those transferred from another healthcare facility were excluded.

The IMPACT prediction rule (a claims-based in-hospital mortality logistic regression prediction rule initially derived in a large US MarketScan commercial and Medicare claims database) was then evaluated in an all-payer inpatient claims only database [8]: $f(x) = 1/(1+\exp(-x))$; where $x = -5.833+(0.026*\text{age})+(0.402*\text{myocardial infarction})+(0.368*\text{chronic lung disease})+(0.464*\text{stroke})+(0.638*\text{prior major bleeding})+(0.298*\text{atrial fibrillation})+(1.061*\text{cognitive impairment})+(0.554*\text{heart failure})+(0.364*\text{renal failure})+(0.484*\text{liver disease})+(0.523*\text{coagulopathy})+(1.068*\text{cancer})$. The 11 comorbidities in the above equation, which were originally calculated using inpatient and outpatient claims data occurring anytime within 12-months before an index PE event, were calculated based only upon the maximum of 25 ICD-9-CM diagnosis codes and 25 procedural codes reported for each discharge in the NIS. When possible, the presence or absence of comorbidities were determined using AHRQ's 29-comorbidity index coding software [10,11]. A key aspect of AHRQ 29-comorbidity coding is the use of a diagnosis-related group (DRG) screen in addition to traditional ICD-9-CM coding. This DRG screen allows comorbidities to be considered as coexisting medical conditions not directly related to the principal diagnosis or the main reason for admission (likely existing prior to the index hospital stay). As the comorbidities of prior major bleeding, cognitive dysfunction, stroke, myocardial infarction (MI) and atrial fibrillation (AF) are not part of the AHRQ 29-comorbidity schema, we coded these variables using ICD-9-CM diagnosis and procedural codes and implemented a similar DRG screen methodology **(Appendix 1)**.

Patients were classified as being low-risk for in-hospital mortality if their predicted in-hospital mortality risk using the above equation was ≤1.5% (a threshold defined in the original derivation study based upon area under the receiver operating characteristic curve (AUC) analysis and a review of prior clinical PE in-hospital mortality rules)[4,8]. To quantify the accuracy of IMPACT for predicting in-hospital mortality in low- and higher-risk PE patients, we calculated sensitivity (the percentage of patients at high-risk for in-hospital mortality who are correctly identified as being high-risk as evidenced by in-

hospital death occurring), specificity (the percentage of patients at low-risk of in-hospital mortality who are correctly identified as being low-risk as evidenced by survival to discharge), positive predictive value (PPV; the probability that in the case of being classified as high-risk for in-hospital mortality, the patient dies prior to discharge) and negative predictive value (NPV; the probability that in the case of being classified as low-risk for in-hospital death, the patient survives to discharge) along with 95% confidence intervals (CIs). The area under the receiver operating characteristic curve (AUC) was calculated to assess the rule's discriminative power to correctly predict inpatient mortality.

We defined an abbreviated hospital stay as ≤1-, ≤2- or ≤3-days based upon values utilized in previous studies [12], and determined the proportion of patients in this category. In order to estimate the potential cost savings from an early discharge, we calculated the difference in total hospital costs between low-risk patients having and not having an abbreviated hospital stay. Total hospital costs were estimated from total hospital charges reported in the NIS using supplied cost-to-charge ratios [10].

All data management and statistical analyses were performed using SAS version 9.2 (SAS Institute Inc., Cary, NC) or IBM SPSS Statistics version 22.0 (IBM Corp., Armonk, NY). Categorical comparisons were made using Pearson's chi-square tests and continuous comparisons were made using either an independent samples t-tests or Mann-Whitney U tests (where appropriate). A p-value <0.05 for considered statistically significant in all situations. Preparation of this report was in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement [13].

RESULTS

A total of 34,108 PE admissions were included in this analysis; 97.7% had a primary ICD-9-CM code for PE. Characteristics of patients at baseline are reported in **Table 1**.

The overall in-hospital PE case-fatality rate was 3.4%. The IMPACT prediction rule classified 11,025 (32.3%) patient admissions as low-risk, and low-risk patients had significantly lower in-hospital mortality (odds reduction of 83%; odds ratio, 0.17, 95%CI=0.13-0.21), shorter LOSs (-1.2 days, p<0.001) and lower total treatment costs (-$3,074, p<0.001) than patients classified as higher-risk **(Table 2)**. Of low-risk patients, 13.1%, 31.1% and 47.7% were discharged within 1, 2 and 3 days of admission. Low-risk patients discharged within 1 day accrued $5,465, 95%CI=$5,018-$5,911 less in treatment costs than those staying longer. Discharge within 2 or 3 days in low-risk patients was also associated with a reduced cost of hospital treatment ($5,820, 95%CI=$5,506-$6,133 and$6,314, 95%CI=$6,031-$6,597, respectively) when compared to those staying longer.

The sensitivity and specificity of IMPACT for prognosticating in-hospital mortality was 92.4%, 95%CI=90.7-93.8 and 33.2%, 95%CI=32.7-33.7, respectively **(Table 3)**. IMPACT's high NPV (>99%) suggests the probability of in-hospital death in those it classifies as low-risk is low, but its low PPV (4.6) suggests it will classify patients who will survive to discharge as high-risk (anticipated to die in-hospital). The AUC of IMPACT was 0.74, 95%CI=0.73-0.76.

DISCUSSION

The IMPACT prediction rule originally developed by Coleman and colleagues [8] in a large US, commercial claims database remained valid when adapted for use in the NIS all-payer, inpatient only claims database. This rule classified in-hospital mortality risk with high sensitivity (and a high NPV), but modest specificity; meaning it classified nearly all patients who died during the index PE admission into the higher-risk group, but also classified patients who survived to discharge as high-risk (also supported by the small PPV indicating that may of the patients classified as high-risk were false positives). While any prediction rules would ideally be 100% sensitive and specific, high sensitivity is preferable to high specificity when making the decision to discharge a PE patient early from the hospital or treat them on

an outpatient basis. Moreover, the observed sensitivity, specificity and proportion of patients deemed to be at low-risk for early mortality when using the IMPACT prediction rule was on par with that seen with the PESI, sPESI and Hestia rules [4]. Despite IMPACT having similar prognostic accuracy to previously developed clinical rules, we strongly suggest the claims-based rule not be used to make treatment decisions, as it was not developed in a clinical setting. The true value of the IMPACT rule is as a benchmarking tool for payers and hospitals to quickly and inexpensively benchmark population rates of PE treated at home or following an abbreviated hospital admission; as well as, to assure high-risk patients are receiving the adequate duration (prolonged) in-hospital treatment.

The IMPACT benchmarking rule has significant potential value due to the common and expensive nature of treating PE in-hospital. There are ~181,000 admissions for PE yearly in the US, with a mean LOS of >5 days and hospital treatment costs >$10,000/admission [1, 10]. Importantly, our analysis found only 13.1% of patients classified as low-risk for in-hospital death were discharged within 1 day, of admission, 31.1% within 2 days and <50% were discharged within 3 days. Even though IMPACT was not 100% accurate, and there are valid reasons why clinicians might not discharge a PE patient early (e.g., need for adequate home circumstances and medication adherent patients [2,3]); when compared to recent studies performed in Canada where ~50% of PE patients were treated as outpatients [14-16]; our data suggests many PE patients treated at US hospitals maybe kept in house longer than medically necessary. Since data from this study suggests a low-risk patient discharged within 3 days has less than half the hospital costs compared to a low-risk patient staying >3 days, we believe there are significant cost savings opportunities to institutions and the healthcare system by assuring PE patients are safely discharged as soon as possible.

A strength of the IMPACT rule, and subsequently our analysis, was our use of the validated AHRQ 29-comorbidity software/Elixhauser coding schema whenever possible [10,11]. This ICD-9-CM coding

schema for comorbidities has been demonstrated to be the best predictor of in-hospital mortality among common comorbidity indices for administrative data [17]. The AHRQ 29-comorbidity software itself codes for 29 comorbidities; of which, 8 comorbidities were included in IMPACT. A key aspect of AHRQ-29 coding is the use of a DRG screen so that comorbidities can be considered coexisting medical conditions not directly related to the principal diagnosis or the main reason for admission, and thus, likely existing prior to the index hospital stay.

Our analysis has some limitations. First, due to the unavailability of out-of-hospital mortality data in the NIS, we could not evaluate 30-day mortality like some previous clinical rules/scores [4]. However, most commercial claims databases and hospitals will also not have broad access to out-of-hospital mortality status. It has been long appreciated the highest risk of complications or death due to PE is in the first few hours to a week after diagnosis [18-21]. Moreover, the sensitivity of clinical prediction rules such as PESI do not vary when used to predict in-hospital or 30-day mortality [5,22,23] For these reasons, in-hospital mortality seems a reasonable endpoint for assessing whether a patient is a good candidate for early discharge (or outpatient treatment). Second, as with all claims databases, the NIS may contain inaccuracies or omissions in coded diagnoses/procedures, leading to the potential for misclassification bias. Finally, the use of 1.5% as a cut-point for low-risk was somewhat arbitrary. The 1.5% value was chosen based upon review of the ROC curve and because it approximates the in-hospital mortality rate seen in PE patients at very low- and low-risk (class I and II) in the original PESI derivation study [5].

CONCLUSION

The IMPACT prediction rule appeared valid when adapted for use in this all-payer, inpatient only administrative claims database. The rule classified patients' mortality risk with high sensitivity; and consequently, may be valuable to those wishing to benchmark rates of PE treated at home or following an abbreviated hospital admission.

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	Total, N (%) N=34,108	Low-Risk, N (%) N=11,025	Higher-Risk, N (%) N=23,083
Age (years, mean±SD)	61.93±17.16	44.21±11.52	70.40±12.24
Male gender	15,953 (46.7)	5,400 (49.0)	10,553 (45.7)
Living in a rural area	2,318 (6.8)	623 (5.7)	1,695 (7.3)
Payer			
Medicare	17,227 (50.6)	1,143 (10.4)	16,084 (69.8)
Medicaid	3,193 (9.4)	1,823 (16.6)	1,370 (5.9)
Private insurance	10,606 (31.2)	6,058 (55.1)	4,548 (19.7)
Self-pay	1,733 (5.1)	1,190 (10.8)	543 (2.4)
No charge	169 (0.5)	123 (1.1)	46 (0.2)
Other	1,109 (3.4)	656 (6.0)	453 (2.0)
Co-morbid diseases, included in claims-based rule			
Myocardial infarction	572 (1.7)	26 (0.2)	546 (2.4)
Chronic lung disease	8,530 (25.0)	1,093 (9.9)	7,437 (32.2)
Cerebrovascular disease (Stroke)	201 (0.6)	9 (0.08)	192 (0.8)
Prior major bleeding	1,167 (3.4)	46 (0.4)	1,121 (4.8)
Atrial fibrillation	3,684 (10.8)	88 (0.08)	3,596 (1.6)
Cognitive impairment (dysfunction)	2,362 (6.9)	1 (0.01)	2,361 (10.2)
Heart failure	4,316 (12.7)	105 (9.5)	4,211 (18.2)
Renal failure	3,420 (10.0)	162 (1.5)	3,258 (14.1)
Liver disease (dysfunction)	774 (2.3)	70 (0.6)	704 (3.0)
Coagulopathy	2,213 (6.5)	172 (1.6)	2,041 (8.8)
Cancer	5,035 (14.8)	4 (0.04)	5,031 (21.8)
Co-morbid diseases; AHRQ-29 comorbidity measure			
Acquired Immune Deficiency Syndrome	90 (0.3)	50 (0.5)	40 (0.2)
Alcohol abuse	1079 (3.2)	425 (3.9)	654 (2.8)
Deficiency anemias	6,653 (19.5)	1,539 (14.0)	5,114 (22.2)
Rheumatoid arthritis/collagen vascular diseases	1,257 (3.7)	352 (3.2)	905 (3.9)
Chronic blood loss anemia	357 (1.0)	121 (1.1)	236 (1.0)
Depression	4,303 (12.6)	1,446 (13.1)	2,857 (12.4)
Diabetes, uncomplicated	6,421 (18.8)	1,326 (12.0)	5,095 (22.1)
Diabetes with chronic complications	983 (2.9)	178 (1.6)	805 (3.5)
Drug abuse	906 (2.7)	536 (4.9)	370 (1.6)
Hypertension	19,655 (57.6)	4,140 (37.6)	15,515 (67.2)
Hypothyroidism	4,438 (13.0)	883 (8.0)	3,555 (15.4)
Lymphoma	481 (1.4)	0 (0)	481 (2.1)
Fluid and electrolyte disorders	7,132 (20.9)	1,466 (13.3)	5,666 (24.5)
Metastatic cancer	2,622 (7.7)	3 (0.03)	2,619 (11.3)
Other Neurological disorders	2,769 (8.1)	534 (4.8)	2,235 (9.7)
Obesity	6,732 (19.7)	2,823 (25.6)	3,909 (16.9)
Paralysis	640 (1.9)	161 (1.5)	479 (2.1)
Peripheral vascular disease	1,722 (5.0)	155 (1.4)	1,567 (6.8)
Psychoses	1,580 (4.6)	719 (6.5)	861 (3.7)
Pulmonary circulation disorders	4,064 (11.9)	867 (7.9)	3,197 (13.9)
Solid tumor without metastasis	1,977 (5.9)	1 (0.01)	1,976 (8.6)
Peptic ulcer disease excluding bleeding	9 (0.03)	4 (0.04)	5 (0.02)
Valvular disease	1,983 (5.8)	281 (2.5)	1,702 (7.4)
Weight loss	1,559 (4.6)	157 (1.4)	1,402 (6.1)

Table 1. Baseline Characteristics for Low-Risk and Higher-Risk Patients

AHRQ=Agency for Healthcare Research and Quality; N=number; SD=standard deviation

	Total, N (%) N=34,108	Low-Risk, N (%) N=11,025	Higher-Risk, N (%) N=23,083	P-Value*
In-hospital mortality	1,158 (3.4)	88 (0.8)	1,070 (4.6)	<0.001
Total treatment cost (mean±SD)	$10,976±12,240	$8,899±8,344	$11,972±13,610	<0.001
Length of stay (days, mean±SD)	5.2±4.5	4.3±3.3	5.6±4.9	<0.001
≤1 day (%)†	3,160 (9.6)	1,430 (13.1)	1,730 (7.9)	<0.001
≤2 days (%)†	7,791 (23.6)	3,3397 (31.1)	4,394 (20.0)	<0.001
≤3 days (%)†	12,715 (38.6)	5,215 (47.7)	7,500 (34.1)	<0.001

Table 2. Comparison of Outcomes Between Patients Classified as Low- and Higher-Risk by the IMPACT Prediction Rule

IMPACT=In-hospital Mortality for Pulmonary embolism using Claims data; N=number; SD=standard deviation

*p-value for the comparison between low- and higher-risk groups

†Calculated only when surviving to discharge

Test Characteristic	Result (95%CI)
Sensitivity, %	92.4 (90.7-93.8)
Specificity, %	33.2 (32.7-33.7)
PPV, %	4.6 (4.4-4.9)
NPV, %	99.2 (99.0-99.4)
AUC	0.74 (0.73-0.76)

Table 3. Test Characteristics for the IMPACT Rule for Predicting In-Hospital Mortality

AUC=area under the receiver operator characteristic curve; CI=confidence interval; IMPACT=In-hospital Mortality for Pulmonary embolism using Claims data; NPV=negative predictive value; PPV=positive predictive value

Appendix 1. International Classification of Diseases, ninth edition, Clinical Modification (ICD-9-CM)* and Diagnosis-Related Group Codes Used to Identify Comorbidities Not Included in the Agency for Healthcare Research and Quality-29 Comorbidity Measure

Myocardial infarction: 41000, 41001, 41002, 41010, 41011, 41012, 41020, 41021, 41022, 41030, 41031, 41032, 41040, 41041, 41042, 41050, 41051, 41052, 41060, 41061, 41062, 41070, 41071, 41072, 41080, 41081, 41082, 41090, 41091, 41092, 41200

Excluding DRGs: 280-285

Atrial fibrillation: 42731

Excluding DRGs: 208-210

Stroke: 43301, 43311, 43321, 43331, 43381, 43391, 43401, 43411, 43491, 4371, 4373

Excluding DRGs: 61-63, 67-68

Cognitive dysfunction: 2900, 2901, 29010, 29012, 29013, 2902, 29020, 29021, 2903, 2904, 29040, 29041, 29042, 29043, 2908, 2909, 2941, 29410, 29411, 2942, 29420, 29421, 2948, 3310, 3311, 33111, 33119, 3312, 33182, 33183, 4380, 78001, 78002, 78009, 78093, 78097, 797, 7970, 9070

Major bleeding: 430, 4300, 431, 4310, 4320, 4321, 4329, 8520, 85200, 85201, 85202, 85203, 85204, 85205, 85206, 85209, 8521, 85210, 85211, 85212, 85213, 85214, 85215, 85216, 85219, 8522, 85220, 85221, 85222, 85223, 85224, 85225, 85226, 85229, 8523, 85230, 85231, 85232, 85233, 85234, 85235, 85236, 85239, 8524, 85240, 85241, 85242, 85243, 85244, 85245, 85246, 85249, 8525, 85250, 85251, 85252, 85253, 85254, 85255, 85256, 85259, 8530, 85300, 85301, 85302, 85303, 85304, 85305, 85306, 85309, 8531, 85310, 85311, 85312, 85313, 85314, 85315, 85316, 85319, 4552, 4555, 4558, 4560, 45620, 4590, 5307, 53082, 53100, 53101, 53120,53121, 53140, 53141, 53160,53161, 53200, 53201, 53220, 53221, 53240, 53241, 53260, 53261, 53300, 53301, 53320,55321, 53340, 53341, 53360, 53361, 53400, 53401, 53420, 53421, 53440, 53441, 53460, 53461, 53501, 53511, 53521, 53531, 53541, 53551, 53561, 53783, 56202, 56203, 56212, 56213, 56881, 5693, 56985, 5780, 5781, 5789, 4230, 59381, 5997, 71911, 7847, 7848, 7863

Excluding DRGs: 64-66, 150-151, 377-384

DRG=diagnosis-related group

*Decimal points have been removed from ICD-9-CM codes to accommodate SAS coding

STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1, 3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5,6
Objectives	3	State specific objectives, including any pre-specified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	6
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7, appendix
Bias	9	Describe any efforts to address potential sources of bias	NA
Study size	10	Explain how the study size was arrived at	NA
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7,8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7,8
		(*b*) Describe any methods used to examine subgroups and interactions	7,8
		(*c*) Explain how missing data were addressed	NA
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	NA

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	NA
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 1
		(b) Indicate number of participants with missing data for each variable of interest	NA
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	9
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9, Table 2 and 3
		(*b*) Report category boundaries when continuous variables were categorized	9, Table 2 and 3
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	9
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	9
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	10,11
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11
Generalisability	21	Discuss the generalisability (external validity) of the study results	11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	1

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.
Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Validation of the Multivariable In-Hospital Mortality for Pulmonary Embolism Using Claims Data (IMPACT) Prediction Rule Within an All-Payer Inpatient Administrative Claims Database

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Validation of the Multivariable In-Hospital Mortality for Pulmonary Embolism Using Claims Data (IMPACT) Prediction Rule Within an All-Payer Inpatient Administrative Claims Database

Running title: Validation of the IMPACT Rule

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ABSTRACT

Objective: To validate the multivariable In-hospital Mortality for PulmonAry embolism using Claims daTa (IMPACT) prediction rule, originally developed in a commercial claims database, in a database consisting only of inpatient claims.

Design: Retrospective claims database analysis.

Setting: The 2012 Healthcare Cost and Utilization Project Nationwide Inpatient Sample

Participants: Adult PE admissions were identified by the presence of an appropriate International Classification of Diseases, ninth edition (ICD-9) code either in the primary position or secondary position when accompanied by a primary code for a PE complication. The multivariable IMPACT rule, which includes age and 11 comorbidities, was used to estimate patients' probability of in-hospital mortality and classify them as low- or higher-risk (≤1.5% deemed low-risk).

Primary and secondary outcome measures: The rule's sensitivity, specificity, positive and negative predictive values (PPV and NPV) and area under the receiver operating characteristic curve (AUC) statistic for predicting in-hospital mortality with accompanying 95% confidence intervals (CIs).

Results: A total of 34,108 admissions for PE were included; with a 3.4% in-hospital case-fatality rate. IMPACT classified 11,025 (32.3%) patients as low-risk; and low-risk patients had significantly lower in-hospital mortality (odds ratio, 0.17, 95%CI=0.13-0.21), shorter LOSs (-1.2 days, p<0.001) and lower total treatment costs (-$3,074, p<0.001) than patients classified as higher-risk. IMPACT had a sensitivity of 92.4%, 95% confidence interval (CI)=90.7-93.8 and specificity of 33.2%, 95%CI=32.7-33.7 for classifying mortality risk. It had a high NPV (>99%), low PPV (4.6%) and an AUC of 0.74, 95%CI=0.73-0.76.

Conclusion: The IMPACT rule appeared valid when used in this all-payer, inpatient only administrative claims database. Its high sensitivity and NPV suggests the probability of in-hospital death in those classified as low-risk by IMPACT was minimal. IMPACT may be valuable to those wishing to identify PE patients who could safely be treated at home or following an abbreviated hospital admission.

ARTICLE SUMMARY

Strengths and limitations of this study

- Many of the 11 comorbidities of the IMPACT rule were coded for within the claims data using the validated AHRQ 29-comorbidity software/schema.
- Due to the lack of out-of-hospital mortality data in the NIS, we could not evaluate longer-term (30-day) mortality of these patients.
- As with all claims databases, the NIS may contain inaccuracies or omissions in coded diagnoses/procedures, leading to the potential for misclassification bias.
- The 1.5% cut-point for defining low-risk for in-hospital mortality can be considered arbitrary; but was chosen (in the original derivation study) based upon review of AUC analysis and previous clinical prediction rules.

The incidence of pulmonary embolism (PE) in US has increased substantially over the past decade; with incidence estimates surpassing 112 PEs per 100,000 Americans [1]. This increased PE incidence has been attributed to improved diagnostic modalities and is associated with a decreased overall case fatality rate. Some have used these data to suggest there are a substantial fraction of PE patients that could potentially be discharged directly from the emergency department, observational unit or from the hospital following an abbreviated stay [1-3]. However, to do so, would require a method for estimating a PE patients' risk of complications, in particular, early mortality.

Numerous clinical prediction rules for prospectively estimating PE patient's short-term mortality have been developed [4]. The PE Severity Index (PESI) [5], simplified PESI (sPESI) [6] and Hestia [7] scores are among the most sensitive for classifying early mortality risk; and suggest at least one-third of all PE patients could be treated at home or following an abbreviated admission [4]. A common theme of these prediction rules is their use of vital signs and laboratory values in addition to comorbidity status [4]. For this reason, these rules cannot be implemented in most administrative claims databases. In the current era of cost-conscious healthcare, there is a growing need for a benchmarking rule that payers and hospitals can use to assess whether they are providing optimal and efficient acute care for patients presenting with PE.

Coleman and colleagues derived such a multivariable benchmarking rule for in-hospital PE mortality using a large, US commercial claims database [8]. This prediction rule, dubbed the In-hospital Mortality for Pulmonary embolism using Claims data (IMPACT), consists of 11 comorbidities identified using in- or outpatient claims data during the 12-months prior to the index PE event (plus age as a continuous variable) and was demonstrated to have a sensitivity and specificity similar to PESI and sPESI [4]. However, because there are many hospital-specific and commercial claims databases which contain

only data from inpatient admissions [9], they contain insufficient claims data to identify relevant comorbidities to populate the above-mentioned rule.

The aim of this study was to determine whether the validity of the IMPACT prediction rule developed in a commercial claims database remained acceptable when utilized in an inpatient only claims database.

METHODS

We utilized the 2012 Agency for Healthcare Research and Quality Healthcare Cost and Utilization Project Nationwide Inpatient Sample (NIS) for this study [10]. The NIS contains data on hospital inpatient stays and covers all patients, including those with Medicare, Medicaid, private insurance and the uninsured. The 2012 inpatient core file contained data on 7,296,968 hospitalizations occurring between January 1, 2012 and December 31, 2012 and was drawn from 4,378 hospitals within 44 states. As only analysis on de-identified data was performed, our study was exempt from institutional review board oversight.

Patients ≥18 years of age with a diagnosis of PE were identified using International Classification of Diseases, ninth edition, Clinical Modification (ICD-9-CM) codes indicating PE as the primary diagnosis (415.11, 415.12, 415.13 and 415.19). To allow for the inclusion of seriously ill patients with PE, we also included admissions with a secondary diagnosis code for PE and a primary code representing one of the following common complication/treatment of PE: respiratory failure (518.81), cardiogenic shock (785.51), cardiac arrest (427.5), secondary pulmonary hypertension (416.8), syncope (780.2), thrombolysis (99.10) and intubation/mechanical ventilation (96.04, 96.05, 96.70-96.72). Admissions with only a secondary diagnosis of PE and those transferred from another healthcare facility were excluded.

The IMPACT prediction rule (a claims-based in-hospital mortality logistic regression prediction rule initially derived in a large US MarketScan commercial and Medicare claims database) was then evaluated in an all-payer inpatient claims only database [8]: 1/(1+exp(-x); where x = -5.833+(0.026*age)+(0.402*myocardial infarction)+(0.368*chronic lung disease)+(0.464*stroke)+(0.638*prior major bleeding)+(0.298*atrial fibrillation)+(1.061*cognitive impairment)+(0.554*heart failure)+(0.364*renal failure)+(0.484*liver disease)+(0.523*coagulopathy)+(1.068*cancer). The 11 comorbidities in the above equation, which were originally calculated using inpatient and outpatient claims data occurring anytime within 12-months before an index PE event, were calculated based only upon the maximum of 25 ICD-9-CM diagnosis codes and 25 procedural codes reported for each discharge in the NIS. When possible, the presence or absence of comorbidities were determined using AHRQ's 29-comorbidity index coding software [10,11]. A key aspect of AHRQ 29-comorbidity coding is the use of a diagnosis-related group (DRG) screen in addition to traditional ICD-9-CM coding. This DRG screen allows comorbidities to be considered as coexisting medical conditions not directly related to the principal diagnosis or the main reason for admission (likely existing prior to the index hospital stay). As the comorbidities of prior major bleeding, cognitive dysfunction, stroke, myocardial infarction (MI) and atrial fibrillation (AF) are not part of the AHRQ 29-comorbidity schema, we coded these variables using ICD-9-CM diagnosis and procedural codes and implemented a similar DRG screen methodology **(Appendix 1)**.

We performed a calibration analysis [11] by plotting observed outcome (in-hospital mortality) by decile of predictions by the IMPACT multivariable prediction rule. The calibration plot was characterized by an intercept, which indicates the extent predictions are systematically too low or high ('calibration-in-large') (a value=0 is ideal), and a calibration slope, which would be equal to 1.0 in the case of a perfect model.

Patients were classified as being low-risk for in-hospital mortality if their predicted in-hospital mortality risk using the above equation was ≤1.5% (a threshold defined in the original derivation study based upon area under the receiver operating characteristic curve (AUC) analysis and a review of prior clinical PE in-hospital mortality rules)[4,8]. To quantify the accuracy of IMPACT for predicting in-hospital mortality in low- and higher-risk PE patients, we calculated sensitivity (the percentage of patients at high-risk for in-hospital mortality who are correctly identified as being high-risk as evidenced by in-hospital death occurring), specificity (the percentage of patients at low-risk of in-hospital mortality who are correctly identified as being low-risk as evidenced by survival to discharge), positive predictive value (PPV; the probability that in the case of being classified as high-risk for in-hospital mortality, the patient dies prior to discharge) and negative predictive value (NPV; the probability that in the case of being classified as low-risk for in-hospital death, the patient survives to discharge) along with 95% confidence intervals (CIs). The area under the receiver operating characteristic curve (AUC) was calculated to assess the rule's discriminative power to correctly predict inpatient mortality.

We defined an abbreviated hospital stay as ≤1-, ≤2- or ≤3-days based upon values utilized in previous studies [12], and determined the proportion of patients in this category. In order to estimate the potential cost savings from an early discharge, we calculated the difference in total hospital costs between low-risk patients having and not having an abbreviated hospital stay. Total hospital costs were estimated from total hospital charges reported in the NIS using supplied cost-to-charge ratios [10].

All data management and statistical analyses were performed using SAS version 9.2 (SAS Institute Inc., Cary, NC) or IBM SPSS Statistics version 22.0 (IBM Corp., Armonk, NY). Categorical comparisons were made using Pearson's chi-square tests and continuous comparisons were made using either an independent samples t-tests or Mann-Whitney U tests (where appropriate). A p-value <0.05 for

considered statistically significant in all situations. Preparation of this report was in accordance with the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) [13].

RESULTS

A total of 34,108 PE admissions were included in this analysis; 97.7% had a primary ICD-9-CM code for PE. Characteristics of patients at baseline are reported in **Table 1**.

The overall in-hospital PE case-fatality rate was 3.4%. Our calibration analysis demonstrated increasing observed in-hospital mortality risk across the progressively increasing deciles of IMPACT predicted risk, a slope of 0.82 and an intercept of 0.0046 (**Figure 1**). The IMPACT prediction rule classified 11,025 (32.3%) patient admissions as low-risk, and low-risk patients had lower in-hospital mortality (odds reduction of 83%; odds ratio, 0.17, 95%CI=0.13-0.21), shorter LOSs (-1.2 days, p<0.001) and lower total treatment costs (-$3,074, p<0.001) than patients classified as higher-risk **(Table 2)**. Of low-risk patients, 13.1%, 31.1% and 47.7% were discharged within 1, 2 and 3 days of admission. Low-risk patients discharged within 1 day accrued $5,465, 95%CI=$5,018-$5,911 less in treatment costs than those staying longer. Discharge within 2 or 3 days in low-risk patients was also associated with a reduced cost of hospital treatment ($5,820, 95%CI=$5,506-$6,133 and$6,314, 95%CI=$6,031-$6,597, respectively) when compared to those staying longer.

The sensitivity and specificity of IMPACT for prognosticating in-hospital mortality was 92.4%, 95%CI=90.7-93.8 and 33.2%, 95%CI=32.7-33.7, respectively **(Table 3)**. IMPACT's high NPV (>99%) suggests the probability of in-hospital death in those it classifies as low-risk is low, but its low PPV (4.6) suggests it will classify patients who will survive to discharge as high-risk (anticipated to die in-hospital). The AUC of IMPACT was 0.74, 95%CI=0.73-0.76 (**Figure 2**).

DISCUSSION

The IMPACT prediction rule originally developed by Coleman and colleagues [8] in a large US, commercial claims database remained valid when adapted for use in the NIS all-payer, inpatient only claims database. This rule classified in-hospital mortality risk with high sensitivity (and a high NPV), but modest specificity; meaning it classified nearly all patients who died during the index PE admission into the higher-risk group, but also classified patients who survived to discharge as high-risk (also supported by the small PPV indicating that may of the patients classified as high-risk were false positives). While any prediction rules would ideally be 100% sensitive and specific, high sensitivity is preferable to high specificity when making the decision to discharge a PE patient early from the hospital or treat them on an outpatient basis. Moreover, the observed sensitivity, specificity and proportion of patients deemed to be at low-risk for early mortality when using the IMPACT prediction rule was on par with that seen with the PESI, sPESI and Hestia rules [4]. Despite IMPACT having similar prognostic accuracy to previously developed clinical rules, we strongly suggest the claims-based rule not be used to make treatment decisions, as it was not developed in a clinical setting. The true value of the IMPACT rule is as a benchmarking tool for payers and hospitals to quickly and inexpensively benchmark population rates of PE treated at home or following an abbreviated hospital admission; as well as, to assure high-risk patients are receiving the adequate duration (prolonged) in-hospital treatment.

The IMPACT benchmarking rule has significant potential value due to the common and expensive nature of treating PE in-hospital. There are ~181,000 admissions for PE yearly in the US, with a mean LOS of >5 days and hospital treatment costs >$10,000/admission [1, 10]. Importantly, our analysis found only 13.1% of patients classified as low-risk for in-hospital death were discharged within 1 day, of admission, 31.1% within 2 days and <50% were discharged within 3 days. Even though IMPACT was not 100% accurate, and there are valid reasons why clinicians might not discharge a PE patient early (e.g.,

need for adequate home circumstances and medication adherent patients [2,3]); when compared to recent studies performed in Canada where ~50% of PE patients were treated as outpatients [14-16]; our data suggests many PE patients treated at US hospitals maybe kept in house longer than medically necessary. Since data from this study suggests a low-risk patient discharged within 3 days has less than half the hospital costs compared to a low-risk patient staying >3 days, we believe there are significant cost savings opportunities to institutions and the healthcare system by assuring PE patients are safely discharged as soon as possible.

A strength of the IMPACT rule, and subsequently our analysis, was our use of the validated AHRQ 29-comorbidity software/Elixhauser coding schema whenever possible [10,11]. This ICD-9-CM coding schema for comorbidities has been demonstrated to be the best predictor of in-hospital mortality among common comorbidity indices for administrative data [17]. The AHRQ 29-comorbidity software itself codes for 29 comorbidities; of which, 8 comorbidities were included in IMPACT. A key aspect of AHRQ-29 coding is the use of a DRG screen so that comorbidities can be considered coexisting medical conditions not directly related to the principal diagnosis or the main reason for admission, and thus, likely existing prior to the index hospital stay.

Our analysis has some limitations. First, due to the unavailability of out-of-hospital mortality data in the NIS, we could not evaluate 30-day mortality like some previous clinical rules/scores [4]. However, most commercial claims databases and hospitals will also not have broad access to out-of-hospital mortality status. It has been long appreciated the highest risk of complications or death due to PE is in the first few hours to a week after diagnosis [18-21]. Despite the fact the in-hospital mortality rate observed in this study (3.4%) is lower than the 30-day mortality rate (~9%) reported in studies of clinical prediction rules such as PESI [5,6]; the sensitivity of clinical prediction rules do not vary markedly when used to predict in-hospital or 30-day mortality [5,22,23] For these reasons, in-hospital mortality seems a

reasonable endpoint for assessing whether a patient is a good candidate for early discharge (or outpatient treatment). Second, as with all claims databases, the NIS may contain inaccuracies or omissions in coded diagnoses/procedures, leading to the potential for misclassification bias. Finally, the use of 1.5% as a cut-point for low-risk was somewhat arbitrary. The 1.5% value was chosen based upon review of the ROC curve (to roughly identify a value balancing sensitivity and specificity) and because it approximates the in-hospital mortality rate seen in PE patients at very low- and low-risk (class I and II) in the original PESI derivation study [5,8].

CONCLUSION

The IMPACT prediction rule appeared valid when adapted for use in this all-payer, inpatient only administrative claims database. The rule classified patients' mortality risk with high sensitivity; and consequently, may be valuable to those wishing to benchmark rates of PE treated at home or following an abbreviated hospital admission.

CONTRIBUTORSHIP STATEMENT

Study concept and design: CGK, CIC, CC, JRS, FWP. Acquisition of data: CIC, CC, JRS. Analysis and interpretation of data: CGK, CIC, CC, JRS, WFP. Drafting of the manuscript: CKG, CIC, FWP. Critical revision of the manuscript for important intellectual content: CIC, CC, JRS, FWP. Administrative, technical, or material support: CIC. CC, JRS. Study supervision: CIC. CGK and CIC had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors read and approved the final manuscript. The authors meet criteria for authorship as recommended by the International Committee of Medical Journal Editors (ICJME) and were fully responsible for all content and editorial decisions, and were involved in all stages of manuscript development.

COMPETING INTEREST

Dr. Coleman has received grant funding and consultancy fees from Janssen Scientific Affairs. LLC, Raritan, NJ, USA; Bayer Pharma AG, Berlin, Germany; and Boehringer-Ingelheim Pharmaceuticals, Inc., Ridgefield, CT, USA. Drs. Crivera and Schein are employees of Janssen Scientific Affairs LLC, Raritan, NJ, USA. Dr. Peacock has received grant funding and consultancy fees from Abbott, Alere, Banyan, Cardiorentis, Janssen, Portola, Roche and The Medicine's Company, Prevencio and Singulex.

FUNDING SOURCE

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DATA SHARING STATEMENT

The 2012 NIS data utilized for this study can be obtained directly from AHRQ.

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FIGURE LEGENDS

Figure 1. Calibration Plot Depicting Observed In-Hospital Mortality By Deciles of IMPACT Estimated In-Hospital Mortality Risk
Error bars represent 95% confidence intervals. The linear relationship depicted by the dotted line is defined by an equation for a straight line with a calibration slope of 0.82 and (calibration slope) an intercept of 0.0046 ('calibration-in-the-large').

Figure 2. Receiver Operating Characteristic Curve for the IMPACT Prediction Rule
The area under the curve for IMPACT was 0.74, 95%CI=0.73-0.76.

	Total, N (%) N=34,108	Low-Risk, N (%) N=11,025	Higher-Risk, N (%) N=23,083
Age (years, mean±SD)	61.93±17.16	44.21±11.52	70.40±12.24
Male gender	15,953 (46.7)	5,400 (49.0)	10,553 (45.7)
Living in a rural area	2,318 (6.8)	623 (5.7)	1,695 (7.3)
Payer			
Medicare	17,227 (50.6)	1,143 (10.4)	16,084 (69.8)
Medicaid	3,193 (9.4)	1,823 (16.6)	1,370 (5.9)
Private insurance	10,606 (31.2)	6,058 (55.1)	4,548 (19.7)
Self-pay	1,733 (5.1)	1,190 (10.8)	543 (2.4)
No charge	169 (0.5)	123 (1.1)	46 (0.2)
Other	1,109 (3.4)	656 (6.0)	453 (2.0)
Co-morbid diseases, included in claims-based rule			
Myocardial infarction	572 (1.7)	26 (0.2)	546 (2.4)
Chronic lung disease	8,530 (25.0)	1,093 (9.9)	7,437 (32.2)
Cerebrovascular disease (Stroke)	201 (0.6)	9 (0.08)	192 (0.8)
Prior major bleeding	1,167 (3.4)	46 (0.4)	1,121 (4.8)
Atrial fibrillation	3,684 (10.8)	88 (0.08)	3,596 (1.6)
Cognitive impairment (dysfunction)	2,362 (6.9)	1 (0.01)	2,361 (10.2)
Heart failure	4,316 (12.7)	105 (9.5)	4,211 (18.2)
Renal failure	3,420 (10.0)	162 (1.5)	3,258 (14.1)
Liver disease (dysfunction)	774 (2.3)	70 (0.6)	704 (3.0)
Coagulopathy	2,213 (6.5)	172 (1.6)	2,041 (8.8)
Cancer	5,035 (14.8)	4 (0.04)	5,031 (21.8)
Co-morbid diseases; AHRQ-29 comorbidity measure			
Acquired Immune Deficiency Syndrome	90 (0.3)	50 (0.5)	40 (0.2)
Alcohol abuse	1079 (3.2)	425 (3.9)	654 (2.8)
Deficiency anemias	6,653 (19.5)	1,539 (14.0)	5,114 (22.2)
Rheumatoid arthritis/collagen vascular diseases	1,257 (3.7)	352 (3.2)	905 (3.9)
Chronic blood loss anemia	357 (1.0)	121 (1.1)	236 (1.0)
Depression	4,303 (12.6)	1,446 (13.1)	2,857 (12.4)
Diabetes, uncomplicated	6,421 (18.8)	1,326 (12.0)	5,095 (22.1)
Diabetes with chronic complications	983 (2.9)	178 (1.6)	805 (3.5)
Drug abuse	906 (2.7)	536 (4.9)	370 (1.6)
Hypertension	19,655 (57.6)	4,140 (37.6)	15,515 (67.2)
Hypothyroidism	4,438 (13.0)	883 (8.0)	3,555 (15.4)
Lymphoma	481 (1.4)	0 (0)	481 (2.1)
Fluid and electrolyte disorders	7,132 (20.9)	1,466 (13.3)	5,666 (24.5)
Metastatic cancer	2,622 (7.7)	3 (0.03)	2,619 (11.3)
Other Neurological disorders	2,769 (8.1)	534 (4.8)	2,235 (9.7)
Obesity	6,732 (19.7)	2,823 (25.6)	3,909 (16.9)
Paralysis	640 (1.9)	161 (1.5)	479 (2.1)
Peripheral vascular disease	1,722 (5.0)	155 (1.4)	1,567 (6.8)
Psychoses	1,580 (4.6)	719 (6.5)	861 (3.7)
Pulmonary circulation disorders	4,064 (11.9)	867 (7.9)	3,197 (13.9)
Solid tumor without metastasis	1,977 (5.9)	1 (0.01)	1,976 (8.6)
Peptic ulcer disease excluding bleeding	9 (0.03)	4 (0.04)	5 (0.02)
Valvular disease	1,983 (5.8)	281 (2.5)	1,702 (7.4)
Weight loss	1,559 (4.6)	157 (1.4)	1,402 (6.1)

Table 1. Baseline Characteristics for Low-Risk and Higher-Risk Patients

AHRQ=Agency for Healthcare Research and Quality; N=number; SD=standard deviation

	Total, N (%) N=34,108	Low-Risk, N (%) N=11,025	Higher-Risk, N (%) N=23,083	P-Value*
In-hospital mortality	1,158 (3.4)	88 (0.8)	1,070 (4.6)	<0.001
Total treatment cost (mean±SD)	$10,976±12,240	$8,899±8,344	$11,972±13,610	<0.001
Length of stay (days, mean±SD)	5.2±4.5	4.3±3.3	5.6±4.9	<0.001
within 1 day (%)†	3,160 (9.6)	1,430 (13.1)	1,730 (7.9)	<0.001
within 2 days (%)†	7,791 (23.6)	3,397 (31.1)	4,394 (20.0)	<0.001
within 3 days (%)†	12,715 (38.6)	5,215 (47.7)	7,500 (34.1)	<0.001

Table 2. Comparison of Outcomes Between Patients Classified as Low- and Higher-Risk by the IMPACT Prediction Rule

IMPACT=In-hospital Mortality for Pulmonary embolism using Claims data; N=number; SD=standard deviation

*p-value for the comparison between low- and higher-risk groups

†Calculated only when surviving to discharge

Test Characteristic	Estimate (95%CI)
Sensitivity, %	92.4 (90.7-93.8)
Specificity, %	33.2 (32.7-33.7)
PPV, %	4.6 (4.4-4.9)
NPV, %	99.2 (99.0-99.4)
AUC	0.74 (0.73-0.76)

Table 3. Test Characteristics for the IMPACT Rule for Predicting In-Hospital Mortality

AUC=area under the receiver operator characteristic curve; CI=confidence interval; IMPACT=In-hospital Mortality for Pulmonary embolism using Claims data; NPV=negative predictive value; PPV=positive predictive value

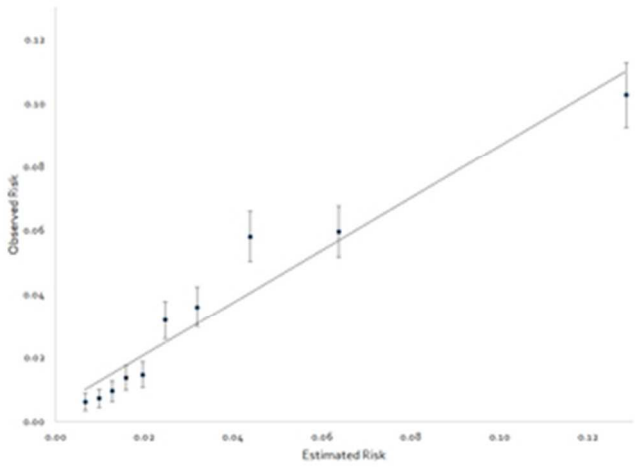

Figure 1. Calibration Plot Depicting Observed In-Hospital Mortality By Deciles of IMPACT Estimated In-Hospital Mortality Risk

Error bars represent 95% confidence intervals. The linear relationship depicted by the dotted line is defined by an equation for a straight line with a calibration slope of 0.82 and (calibration slope) an intercept of 0.0046 ('calibration-in-the-large').

27x20mm (300 x 300 DPI)

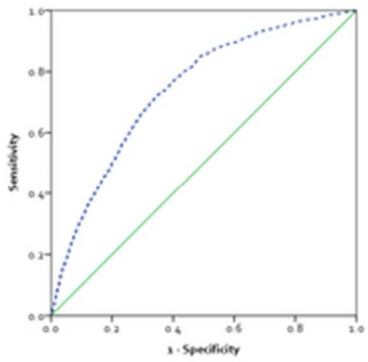

Figure 2. Receiver Operating Characteristic Curve for the IMPACT Prediction Rule
The area under the curve for IMPACT was 0.74, 95%CI=0.73-0.76.

21x17mm (300 x 300 DPI)

SUPPLEMENTARY FILE

Appendix 1. International Classification of Diseases, ninth edition, Clinical Modification (ICD-9-CM)* and Diagnosis-Related Group Codes Used to Identify Comorbidities Not Included in the Agency for Healthcare Research and Quality-29 Comorbidity Measure

Myocardial infarction: 41000, 41001, 41002, 41010, 41011, 41012, 41020, 41021, 41022, 41030, 41031, 41032, 41040, 41041, 41042, 41050, 41051, 41052, 41060, 41061, 41062, 41070, 41071, 41072, 41080, 41081, 41082, 41090, 41091, 41092, 41200

Excluding DRGs: 280-285

Atrial fibrillation: 42731

Excluding DRGs: 208-210

Stroke: 43301, 43311, 43321, 43331, 43381, 43391, 43401, 43411, 43491, 4371, 4373

Excluding DRGs: 61-63, 67-68

Cognitive dysfunction: 2900, 2901, 29010, 29012, 29013, 2902, 29020, 29021, 2903, 2904, 29040, 29041, 29042, 29043, 2908, 2909, 2941, 29410, 29411, 2942, 29420, 29421, 2948, 3310, 3311, 33111, 33119, 3312, 33182, 33183, 4380, 78001, 78002, 78009, 78093, 78097, 797, 7970, 9070

Major bleeding: 430, 4300, 431, 4310, 4320, 4321, 4329, 8520, 85200, 85201, 85202, 85203, 85204, 85205, 85206, 85209, 8521, 85210, 85211, 85212, 85213, 85214, 85215, 85216, 85219, 8522, 85220, 85221, 85222, 85223, 85224, 85225, 85226, 85229, 8523, 85230, 85231, 85232, 85233, 85234, 85235, 85236, 85239, 8524, 85240, 85241, 85242, 85243, 85244, 85245, 85246, 85249, 8525, 85250, 85251, 85252, 85253, 85254, 85255, 85256, 85259, 8530, 85300, 85301, 85302, 85303, 85304, 85305, 85306, 85309, 8531, 85310, 85311, 85312, 85313, 85314, 85315, 85316, 85319, 4552, 4555, 4558, 4560, 45620, 4590, 5307, 53082, 53100, 53101, 53120,53121, 53140, 53141, 53160,53161, 53200, 53201, 53220, 53221, 53240, 53241, 53260, 53261, 53300, 53301, 53320,55321, 53340, 53341, 53360, 53361, 53400, 53401, 53420, 53421, 53440, 53441, 53460, 53461, 53501, 53511, 53521, 53531, 53541, 53551, 53561, 53783, 56202, 56203, 56212, 56213, 56881, 5693, 56985, 5780, 5781, 5789, 4230, 59381, 5997, 71911, 7847, 7848, 7863

Excluding DRGs: 64-66, 150-151, 377-384

DRG=diagnosis-related group

*Decimal points have been removed from ICD-9-CM codes to accommodate SAS coding

STROBE 2007 (v4) checklist of items to be included in reports of observational studies in epidemiology*

Checklist for cohort, case-control, and cross-sectional studies (combined)

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1, 3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5,6
Objectives	3	State specific objectives, including any pre-specified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants	6
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7, appendix
Bias	9	Describe any efforts to address potential sources of bias	NA
Study size	10	Explain how the study size was arrived at	NA
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	7,8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7,8
		(*b*) Describe any methods used to examine subgroups and interactions	7,8
		(*c*) Explain how missing data were addressed	NA
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed	NA

		Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	NA
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 1
		(b) Indicate number of participants with missing data for each variable of interest	NA
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)	NA
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	9
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	9, Table 2 and 3
		(*b*) Report category boundaries when continuous variables were categorized	9, Table 2 and 3
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	9
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	9
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	10,11
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11
Generalisability	21	Discuss the generalisability (external validity) of the study results	11
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	1

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.