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Keywords:	Inpatient mortality, emergency department, predictive model, electronic health records

A Novel Model for Predicting Inpatient Mortality after Emergency Admission to Hospital in Singapore

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Abstract

Objectives: To identify risk factors for inpatient mortality after patients' emergency admission and create a novel model predicting inpatient mortality risk.

Design: This was a retrospective observational study using data extracted from the electronic health records (EHR). The data was randomly split into a derivation set and a validation set. The stepwise model selection was employed. We compared our model with one of the current clinical scores, Cardiac Arrest Risk Triage (CART) score.

Setting: A single tertiary hospital in Singapore.

Participants: All adult hospitalized patients, admitted via ED from Jan 1, 2008, to Oct 31, 2017 (n= 433,187 by admission episodes)

Main outcome measure: The primary outcome of interest was inpatient mortality following this admission episodes. The Area Under the Curve (AUC) of the operating characteristic curve (ROC) of the predictive model with sensitivity and specificity for optimized cut-offs.

Results: 15,758 (3.64%) of the episodes were observed inpatient mortality. 19 variables were observed as significant predictors and included in our final regression model. Our predictive model outperformed the CART score in terms of predictive power. The AUC of CART score and our final model was 0.705 (95% CI: 0.697-0.714) and 0.817 (95% CI: 0.810-0.824) respectively.

Conclusion: We developed and validated a model for inpatient mortality using EHR data collected in the ED. The performance of our model was more accurate than the CART score. Implementation of our model in the hospital can potentially predict imminent adverse events and institute appropriate clinical management.

Keywords: Inpatient mortality, emergency department (ED), predictive model, electronic health records (EHR)

Strengths and limitations of this study

- Study identified several risk factors and developed a novel model was for predicting future risk of inpatient mortality based on features collected at ED.
- Large EHR database and high predictive power
- Single site study without external validation

Introduction

Inpatient mortality, a key performance indicator of health services, provides general information concerning patient care delivery. Despite decades of research, inpatient mortality remains an issue [1-3]. Lu et al. showed that preventable deaths in emergency admitted patients with early mortality are not rare[4]. The Harvard Medical Practice Study I estimated 27.6% of the adverse events as a result of negligence [5]. Even a delay of a few hours in transferring critically ill patients to the intensive care unit (ICU) results in increased mortality [6]. Several studies [7-9] have shown that physiological deterioration or abnormal vital signs before cardiac arrest or death were common, making it possible to predict the progression of adverse events. Previous intervention studies have demonstrated that inpatient mortality can be avoided by adequate care [10], frequent physiological measurement [11] or other necessary measures. However, few studies managed to model the risk factors related to inpatients mortality after patients' emergency admission through the emergency department (ED). Therefore, we proposed to utilize medical features collected at the ED to conduct predictive analysis, anticipating imminent adverse events and thus allowing physicians to respond appropriately.

There are numerous models for detecting mortality in the hospital, including the Early Warning Scores (EWS) system [12], which have been implemented in many hospitals to recognize early clinical deterioration. The concept of EWS was proposed by Morgan et al. in 1997 and it included mainly the vital signs variables such as heart rate, blood pressure, respiratory rate, temperature and neurological status [13]. Subsequently, multiple variants have been developed, such as NEWS [14], Modified EWS (MEWS) [15] and VitalPAC™ EWS (ViEWS) [16]. The adoption of EWS in the hospital was found to correlate with reduced mortality rates and improved overall patient outcomes in a systematic review [17]. However, several studies [18-20] pointed out its limitations such as over-sensitivity, low specificity, and the need for accompanying critical care outreach team. Accordingly, there still is a need for improvement in accurate recognition. In 2012, the Cardiac Arrest Risk Triage (CART) score was developed with higher predictive power and usability than the MEWS [21]. Furthermore, the increasing popularity of electronic health records (EHR) [22] creates an opportunity to acquire a more comprehensive and usable model for risk stratification in hospital. Besides patient factors, non-patient factors including prolonged emergency boarding [23] , ED overcrowding [24] and day of week [25] were utilized to augment the model's sensitivity and specificity. Despite the common view of these worthwhile interventions, few clinical trials demonstrated a consistent improvement in reducing the hospital-wide mortality rate.

Currently, there are few studies on early risk stratification of ED patients for in-patient mortality in Singapore. A study in the United States [26] has focused on patients with a specific diagnosis. Increased age, low systolic blood pressure or sodium levels, elevated heart rate or creatinine at admission were identified as important predictors for inpatient mortality in patients hospitalized for heart failure. However, few studies report the general risk of inpatient mortality from the information gathered when patients are presented to the ED in Singapore. In this study, we aimed to derive and validate a mortality prediction model from the available information commonly collected in the ED, assisting doctors in identifying high-risk patients.

Methods

Study design and setting

We performed a retrospective, single-center study to derive a novel model to predict inpatient mortality in wards using routinely collected data in the ED and compared its accuracy to the CART score. Singapore is a city-state in Southeast Asia with 5.6 million people and diverse ethical composition. Its mixed healthcare system provides affordable care funded through both compulsory savings and partial subsidies. The site of this study is Singapore General Hospital (SGH), the largest and oldest tertiary hospital with more than 30 clinical disciplines and 1700 inpatient beds. Its ED receives over 120,000 visits and refers 36,000 inpatient admissions annually. EHR data was obtained from Singapore Health Services and employed in this study. This study was approved by Singapore Health Services' Centralized Institutional Review Board where patient consent was waived.

Patient and public involvement

No patient involved.

Study population and outcome

All patients visiting the ED from January 1, 2008 until October 31, 2017 who were subsequently admitted after their ED discharge across all clinical specialties in SGH were included in this study. We excluded patients who were below 21 years old and died in the ED. The primary outcome of interest was inpatient mortality, identified by hospital's admission and discharge administrative database.

Data collection and variables

We extracted data from the hospital's EHR, named as the SingHealth Electronic Health lntelligence System (eHints). Patients' details were deidentified to ensure that data was sufficiently anonymized and simultaneously we need to make sure we could identify the same patients in different repeated visits. Death records were obtained from the national death registry and were matched to specific patients in the hospital. We selected variables that are available in the ED prior to hospital admission to ensure the model is clinically useful for early identification. Selected variables included four demographical variables, four ED administrative variables and eleven clinical variables. Demographic variables include age, gender, nationality, and race. ED administrative variables include consultation waiting time (unit: hour), ED boarding time (unit: hour), day of week, shift time. Among these, ED boarding time is the amount of time that patients spent from consultation to ED discharge. Consultation waiting time is the amount of time that patients spent from ED registration to the first consultation with ED physicians. Clinical variables include one clinical service variable, 6 commonly sampled vital signs and 4 commonly sampled laboratory tests; specifically, they are: blood gas (Yes/No), pulse (beats per minute), respiration rate (breaths per minute), fraction of inspired oxygen (FiO_2), blood oxygen saturation (SPO_2), diastolic blood pressure (mmHg), systolic blood pressure (mmHg), bicarbonate (mmol/L), creatinine (μmol/L), potassium (mmol/L), and sodium (mmol/L).

Statistical analysis

The data was analyzed using R version 3.42 (R Foundation, Vienna, Austria). After confirming the cohort, the data was randomly split into derivation and validation sets.

Derivation set was used to generate the model. Model accuracy was reported on the validation set and bootstrapped samples were applied to calculate 95% confidence intervals (CIs). During this analysis, outliers were kicked off and missing values were imputed using the median value of the derivation dataset on condition that the missing percentage of this column was less than 15%.

Baseline characteristics of the study population were analyzed on both derivation and validation sets to confirm similarity. Descriptive summaries like frequencies and percentage were reported for categorical variables, while means and standard deviations (SDs) were reported for continuous variables. We compared admitted patients with and without inpatient mortality using two-tailed Student's t-test for continuous variables and chi-square test for categorical variables. Because of the large sample size associated with EHRs, the threshold for declaring statistical significance level was set as $p<0.01$, much smaller than the usual 0.05 level, in order to reduce the chances of finding spurious effects.

The prediction model was built by applying two-step logistic regression to the derivation set. Firstly, univariate analysis was performed on all variables to access their independent association to inpatient mortality. The largest cohort of each variable was selected as the baseline for comparison with other groups. Odds ratios (OR) and corresponding CI were calculated. Secondly, variables with $p<0.01$ from the first step were selected to be analyzed using multivariate logistic regression with backward stepwise variable selection.

In the final regression model, the modeling performance was evaluated on the validation set. Our model generated a probability of inpatient mortality from 0 to 1 for each admission episodes. The predictive power of the model was calculated using the area under the curve (AUC) in the receiver operating characteristic (ROC) analysis. In order to compare our model with current clinical scores, we also applied Cardiac Arrest Risk Triage (CART) [21] score into the same validation set and compared the performance between CART score and our novel model.

Results

Basic characteristics

A total of 433,187 unique emergency admission episodes were included in this study. Of the 433,187 eligible episodes, 15,758 episodes (3.64%) met the outcome, i.e. inpatient mortality. The mean age of the whole cohort was 62.1 (SD=17.7) years, 50.1% were female (n=216,914), most patients were Singaporean (90.5%, n=392,219) , the ethnic compositions were similar to population norms (71.2% for Chinese,12.1% for Malay, 10.6% for Indian and 6.1% for others), 2.1% (n=9144) of the patients received blood gas services in the ED, the mean ED boarding time was 4.78 (SD=3.83) hours and the mean ED consultation waiting time was 0.77 (SD=0.79) hours).

The whole cohort was subsequently divided into the derivation and validation set as displayed in Figure 1. Table 1 shows the statistics of highly similar population in both sets. The derivation set was constitutive of patients with a mean age of 62.1 (SD=17.7), with similar male (49.9%) and female (50.1%) proportion, with the ethnic breakdown representing the general Singaporean population. Compared to the patients who survived to discharge, patients who died in hospital were older, had shorter ED

boarding time and consultation waiting time, and a higher probability of receiving blood gas services while in the ED. They also had lower SPO_2, blood pressure, bicarbonate, and sodium concentration with a higher pulse, respiration rate, FiO_2, and potassium and creatinine concentration.

Univariable Analysis

Table 2 shows the OR and adjusted OR of all demographic, administrative and clinical variables. All variables were respectively significant in the univariate regression in terms of the p-value. Observed from the demographical data, patients who were male, Chinese ethnic Singaporean had a higher risk of inpatient mortality. Patients who were foreigners and other races beyond Chinese were unlikely to die in the hospital after emergency admission. Administratively, patients who had shorter consultation waiting time and ED boarding time were more likely to die in hospital. Clinically, patients with a higher pulse, respiration rate, FIO_2, creatinine and potassium concentration and lower blood pressure, SPO_2, bicarbonate, and sodium concentration had a higher risk of inpatient death. All 19 variables were selected for multivariate stepwise analysis as a result of their p-values all below 0.01.

Multivariable Analysis

All variables were used to create the stepwise regression model and no variable was removed through stepwise variable selection. The final model contains 19 variables and the multivariate analysis with the corresponding adjusted odds ratio are shown in Table 2. Older Singaporean with Chinese ethnic had a higher change of inpatient mortality. Although diastolic blood pressure, shift time and day of week were not very significant in multivariate analysis, they were included into the final model after backward stepwise variable selection and due to the clinical judgments [27].

Predictive Model Performance

Our model shows good discriminatory capability on predicting inpatient mortality. On the validation set, the model achieved the AUC of 0.817 (95% CI: 0.810-0.824) with a sensitivity of 72.7% and a specificity of 75.4% under the optimal threshold (Probability = 0.037) as shown in Figure 2. In contrast, the performance of the existing CART score achieved the AUC of 0.705 (95% CI: 0.697-0.714) with the sensitivity (72.1%) and specificity (56.1%) under the optimal threshold (CART value = 8).

Discussion

In this study, the main finding is that 19 routinely collected variables from the ED EHR system can be utilized to predict inpatient mortality for the patients after their emergency admission. Our predictive model has better discriminative power than the CART score (AUC, 0.817 vs. 0.705) on the same validation set. The results suggest the possibility of building a reliable inpatient mortality model from the basic demographic, administrative and limited clinical information acquired in the ED when patients are admitted into the hospital through ED. By deriving a model of inpatient mortality using routinely collected ED data, our study identifies factors associated with inpatient mortality and provides a potentially useful tool for risk stratification of ED patients.

A major strength of our model is the size of the dataset, which was used for deriving this model. This is among the largest datasets used to generate an inpatient mortality predictive model with a cohort of over 430,000 patients in a 10-year period, targeting almost the whole hospital. In addition, it included a large amount of diversity due to Singapore's diverse population. Another advantage of our model is its comprehensiveness, making it applicable to general patient population presenting to the ED rather than some specific patient subgroups. Furthermore, the application of EHR systems will make our model easy to implement.

There are several reasons why the CART score underperformed our novel model in our study. At first, the CART score did not comprise laboratory test variables. The importance of including routine laboratory test values in the risk predictive model has been demonstrated in other studies. For example, in a study [28] by Churpek and colleagues, including laboratory values in his model contributes important knowledge to the field. Pine et al. [29] and Froom et al. [30] also gave evidence of laboratory values improving predictions of hospital mortality. Secondly, CART was unable to make use of valuable routine administrative data. Guttmann et al. [31] and Parker et al. [32] have previously shown that waiting time, work shifts and other administrative variables were greatly associated with inpatient mortality and hospital admission. In comparison, our model takes both ED administrative data and laboratory test value into account, proving a higher accuracy than the CART score.

Previous researchers have created several predictive tools for inpatient mortality. For example, Prytherch et al. [16] developed the ViEWS score, mainly utilizing vital signs variables to predict mortality for hospitalized patients within 24 hours. The significant predictors of mortality were the pulse, breathing rate, temperature, systolic BP, SPO_2, FiO_2 and mental status. Although vital signs are potential predictors of adverse events, it gives rapid response team (RRT) too short time to respond, especially in a hospital with full capacity or lack of manpower. Since changes in vital signs occur hours before the event, these changes may not be seen at the time of consultation at the ED when potentially high-risk patients have non-discriminatory vital signs similar to that of other healthy patients. Secondly, elderly patients may not have the expected vital signs changes associated with the clinical deterioration and modeling using vital signs alone might miss out cases. It was demonstrated in a study [33] of Churpek and colleagues, who suggests additional predictors of adverse events for elderly patients. Our model is notably different from this because it involved laboratory test values and administrative data besides vital signs and were presumably appropriate for the rapidly aging population in Singapore [34].

Another study [35] in Australia employed multivariable logistic regression of variables from datasets obtained at triage in one hospital to derive and validate a mortality prediction model, Triage Information Mortality Model (TIMM). This TIMM included age, gender, time of year, ambulance, Australasian triage scale and nine chief complaint codes. However, it did not include any physiological variables that were considered as strong predictors and could be obtained conveniently from EHR system. In comparison, our model combined demographic, administrative, and physiological variables, which will provide a much more comprehensive profile and capture the sufficient information of the patients in the ED, hence improving the model's predictive power.

Our data analysis also produces some notable findings regarding risk factors related to inpatient mortality. It identified increased age, low blood pressure, high heart rate and elevated creatinine and potassium concentration and decreased sodium and bicarbonate concentration when patients are present to ED as important predictors for inpatient mortality. Besides these factors, our study identified some non-patient factors such as emergency boarding time, day of week and shift time, which can affect patient outcomes. Presenting to ED on Friday or weekend and shift time 24:00 to 8:00 increases risk, potentially as a result of the ED overcrowding, insufficient services, change of shift and slower access to critical investigations. Shorter ED boarding time and consultation waiting time become predictors potentially due to severely critical patients with a fast track to admission and intensive resources.

The information needed for this novel model is readily available at the time of consultation at the ED when the first set of laboratory tests are done. When a physician has to make a decision on further management and disposition of the patient. Our model can be deployed for early identification of high-risk patients. Afterward, we can allocate more intensive resources to high-risk patients with sufficient level of monitoring, increasing nursing attention [36], activation of a rapid response team [37] or medical emergency team (MET) [38]. Thus, through our model, these patients could be seen early after emergency admission and above interventions can be started to avoid severe sudden adverse events during their inpatient stay. Similarly, low-risk patients below the predictive threshold could potentially be safely identified who might not need admission or intensive monitoring and thus save precious in-patient resources. Overall, the good performance, usability and widespread adoption of advanced EHR system make our model easy to integrate into the hospital electronic system such that the probability of inpatient mortality or real-time risk score can be calculated for every patient when they are presented to the ED and ready for admission to hospital. The model can supplement the physician's judgment in decision-making.

Limitation

There are several limitations in this study. First, all variables included in this study are based on EHR and it only contains routinely collected information and does not include all information available when patients are present to the ED. For example, due to the lack of neurological features, we were not able to calculate the MEWS score and compare it with our model. Second, this is a single-site study, which might limit its predictive power when it's applied into other settings. Much work could be done in the future for validating it in different hospital settings in Singapore or other countries.

Conclusion

In summary, we identified several risk factors and developed a novel model for inpatient mortality using 10-year EHR data routinely collected at the ED. The discriminative capability of our model was better than that of the traditional clinical score, CART score. Implementation of our model in the ED can allow accurate and timely identification of a high-risk cohort for interventions during their inpatient stay, resulting in potential reduction in avoidable inpatient mortality.

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Table 1: Description of the study cohort

	Derivation Set				Validation Set			
	All Admission Episodes (n=333,187)	Discharged (n=321,061)	Inpatient Mortality (n=12,126)	p-Value	All Admission Episodes (n=100,000)	Discharged (n=96,368)	Inpatient Mortality (n=3,632)	p-Value
Demographics								
Age (SD)	62.12 (17.67)	61.79 (17.71)	70.78 (13.92)	<0.001	62.12 (17.65)	61.79 (17.69)	70.86 (13.84)	<0.001
Gender (%)				<0.001				<0.001
Male	166354 (49.9)	159742 (49.8)	6612 (54.5)		49892 (49.9)	47902 (49.7)	1990 (54.8)	
Female	166833(50.1)	161319(50.2)	5514(45.5)		50108(50.1)	48466(50.3)	1642(45.2)	
Nationality (%)				<0.001				<0.001
Singaporean	301661(90.5)	290204(90.4)	11457(94.5)		90558(90.6)	87102(90.4)	3456(95.2)	
Foreigner	31526 (9.5)	30857 (9.6)	669 (5.5)		9442 (9.4)	9266 (9.6)	176 (4.8)	
Race (%)				<0.001				<0.001
Chinese	237147 (71.2)	227418 (70.8)	9729 (80.2)		71196 (71.2)	68242 (70.8)	2954 (81.3)	
Malay	40377 (12.1)	39210 (12.2)	1167 (9.6)		12171 (12.2)	11815 (12.3)	356 (9.8)	
Indian	35259 (10.6)	34466 (10.7)	793 (6.5)		10585 (10.6)	10348 (10.7)	237 (6.5)	
Others	20404 (6.1)	19967 (6.2)	437 (3.6)		6048 (6.0)	5963 (6.2)	85 (2.3)	
ED Administrative Data								
Consultation waiting time (SD)	0.77 (0.80)	0.78 (0.80)	0.48 (0.58)	<0.001	0.77 (0.79)	0.78 (0.79)	0.48 (0.57)	<0.001
ED boarding time (SD)	4.78 (3.83)	4.80 (3.83)	4.35 (3.70)	<0.001	4.78 (3.84)	4.80 (3.84)	4.40 (3.94)	<0.001
Day of week (%)				<0.001				0.002
Midweek	144866 (43.5)	139817 (43.5)	5049 (41.6)		43395 (43.4)	41897 (43.5)	1498 (41.2)	
Monday	55643 (16.7)	53726 (16.7)	1917 (15.8)		16659 (16.7)	16088 (16.7)	571 (15.7)	
Friday	46724 (14.0)	44932 (14.0)	1792 (14.8)		13915 (13.9)	13380 (13.9)	535 (14.7)	
Weekend	85954 (25.8)	82586 (25.7)	3368 (27.8)		26031 (26.0)	25003 (25.9)	1028 (28.3)	
Shift time (%)				0.002				0.243
08:00 to 16:00	167802 (50.4)	161871 (50.4)	5931 (48.9)		50514 (50.5)	48729 (50.6)	1785 (49.1)	
16:00 to 24:00	125745 (37.7)	121075 (37.7)	4670 (38.5)		37896 (37.9)	36480 (37.9)	1416 (39.0)	

24:00 to 8:00	39640 (11.9)	38115 (11.9)	1525 (12.6)		11590 (11.6)	11159 (11.6)	431 (11.9)	
Clinical Data								
Blood gas (%)	6971 (2.1)	6047 (1.9)	924 (7.6)	<0.001	2173 (2.2)	1889 (2.0)	284 (7.8)	<0.001
Pulse (SD)	82.70 (17.02)	82.28 (16.69)	93.85 (21.32)	<0.001	82.71 (16.98)	82.32 (16.66)	93.21 (21.44)	<0.001
Respiration rate (SD)	17.85 (1.74)	17.81 (1.63)	18.81 (3.40)	<0.001	17.84 (1.73)	17.81 (1.63)	18.78 (3.36)	<0.001
FiO_2 (SD)	23.10 (10.14)	22.63 (8.50)	35.43 (27.44)	<0.001	23.07 (10.02)	22.64 (8.46)	34.67 (26.89)	<0.001
SPO_2 (SD)	97.99 (3.18)	98.02 (3.05)	97.14 (5.60)	<0.001	97.98 (3.23)	98.01 (3.07)	97.14 (5.97)	<0.001
Diastolic BP (SD)	71.34 (13.46)	71.49 (13.33)	67.22 (15.81)	<0.001	71.39 (13.55)	71.57 (13.42)	66.65 (15.88)	<0.001
Systolic BP (SD)	133.76 (25.33)	134.12 (25.17)	124.29 (27.58)	<0.001	133.87 (25.44)	134.27 (25.25)	123.16 (27.87)	<0.001
Bicarbonate (SD)	22.80 (3.54)	22.86 (3.43)	21.18 (5.48)	<0.001	22.79 (3.55)	22.85 (3.44)	21.23 (5.44)	<0.001
Creatinine (SD)	146.60 (197.88)	144.91 (197.04)	191.47 (214.24)	<0.001	145.86 (196.34)	144.36 (195.53)	185.80 (212.89)	<0.001
Potassium (SD)	4.16 (0.67)	4.15 (0.66)	4.38 (0.92)	<0.001	4.16 (0.68)	4.15 (0.66)	4.35 (0.89)	<0.001
Sodium (SD)	135.11 (4.85)	135.18 (4.73)	133.29 (7.26)	<0.001	135.12 (4.86)	135.19 (4.72)	133.20 (7.43)	<0.001

ED=Emergency Department, SD= Standard Deviation, ED=Emergency Department, SD= Standard Deviation, BP=Blood Pressure, FiO2= Fraction of inspired oxygen, SPO2= Blood Oxygen Saturation

Table 2: Univariable and multivariable analysis

	Unadjusted OR (95% CI)	p-Value	Adjusted OR (95% CI)	Adjusted p-Value
Demographics				
Age	1.034(1.033-1.035)	<0.001	1.035(1.033-1.036)	<0.001
Gender				
Female	Baseline		Baseline	
Male	1.211(1.168-1.256)	<0.001	1.144(1.1-1.19)	<0.001
Nationality				
Singaporean	Baseline		Baseline	
Foreigner	0.549(0.508-0.594)	<0.001	0.898(0.82-0.984)	0.021
Race				
Chinese	Baseline		Baseline	
Malay	0.696(0.654-0.74)	<0.001	0.865(0.809-0.925)	<0.001
Indian	0.538(0.5-0.579)	<0.001	0.69(0.638-0.746)	<0.001
Others	0.512(0.464-0.564)	<0.001	0.773(0.692-0.862)	<0.001
ED Administrative				
Consultation waiting time	0.437(0.42-0.454)	<0.001	0.683(0.659-0.709)	<0.001
ED boarding time	0.96(0.954-0.966)	<0.001	0.981(0.975-0.987)	<0.001
Day of Week				
Midweek	Baseline		Baseline	
Monday	0.988(0.937-1.042)	0.661	1.009(0.953-1.068)	0.761
Friday	1.104(1.045-1.167)	<0.001	1.084(1.022-1.149)	0.007
Weekend	1.129(1.08-1.181)	<0.001	1.001(0.954-1.051)	0.954
Shift time				
8:00 to 16:00	Baseline		Baseline	
16:00 to 24:00	1.053(1.012-1.095)	0.01	1.023(0.981-1.067)	0.288
24:00 to 8:00	1.092(1.031-1.156)	0.003	0.94(0.883-1)	0.05
Clinical Data				
Blood gas (Yes=1, No=0)	4.297(4-4.617)	<0.001	1.224(1.121-1.336)	<0.001
Pulse	1.035(1.034-1.036)	<0.001	1.025(1.024-1.026)	<0.001
Respiration rate	1.2(1.192-1.208)	<0.001	1.034(1.027-1.042)	<0.001
FiO_2	1.04(1.039-1.04)	<0.001	1.028(1.027-1.029)	<0.001
SPO_2	0.966(0.963-0.969)	<0.001	0.979(0.976-0.983)	<0.001
Diastolic BP	0.975(0.973-0.976)	<0.001	0.999(0.997-1.001)	0.18
Systolic BP	0.984(0.983-0.984)	<0.001	0.985(0.984-0.986)	<0.001
Bicarbonate	0.889(0.885-0.893)	<0.001	0.967(0.962-0.972)	<0.001
Creatinine	1.001(1.001-1.001)	<0.001	1.001(1.001-1.001)	<0.001
Potassium	1.528(1.494-1.562)	<0.001	1.159(1.129-1.189)	<0.001
Sodium	0.938(0.935-0.941)	<0.001	0.961(0.958-0.964)	<0.001

ED=Emergency Department, SD= Standard Deviation, BP=Blood Pressure, OR=Odd Ratio, FiO_2= Fraction of inspired oxygen, SPO_2= Blood Oxygen Saturation

Author Contributions

FX, NL and MEHO conceived and designed the study. NL, MEHO and BC supervised the study. FX, SXW and NL performed data retrieval and preprocessing. FX and NL analyzed the data. FX, NL, YA, LLL, AFWH, SSWL, DBM, MEHO and BC interpreted the results. FX wrote the first draft of the paper and all authors critically revised the paper and gave final approval for publication.

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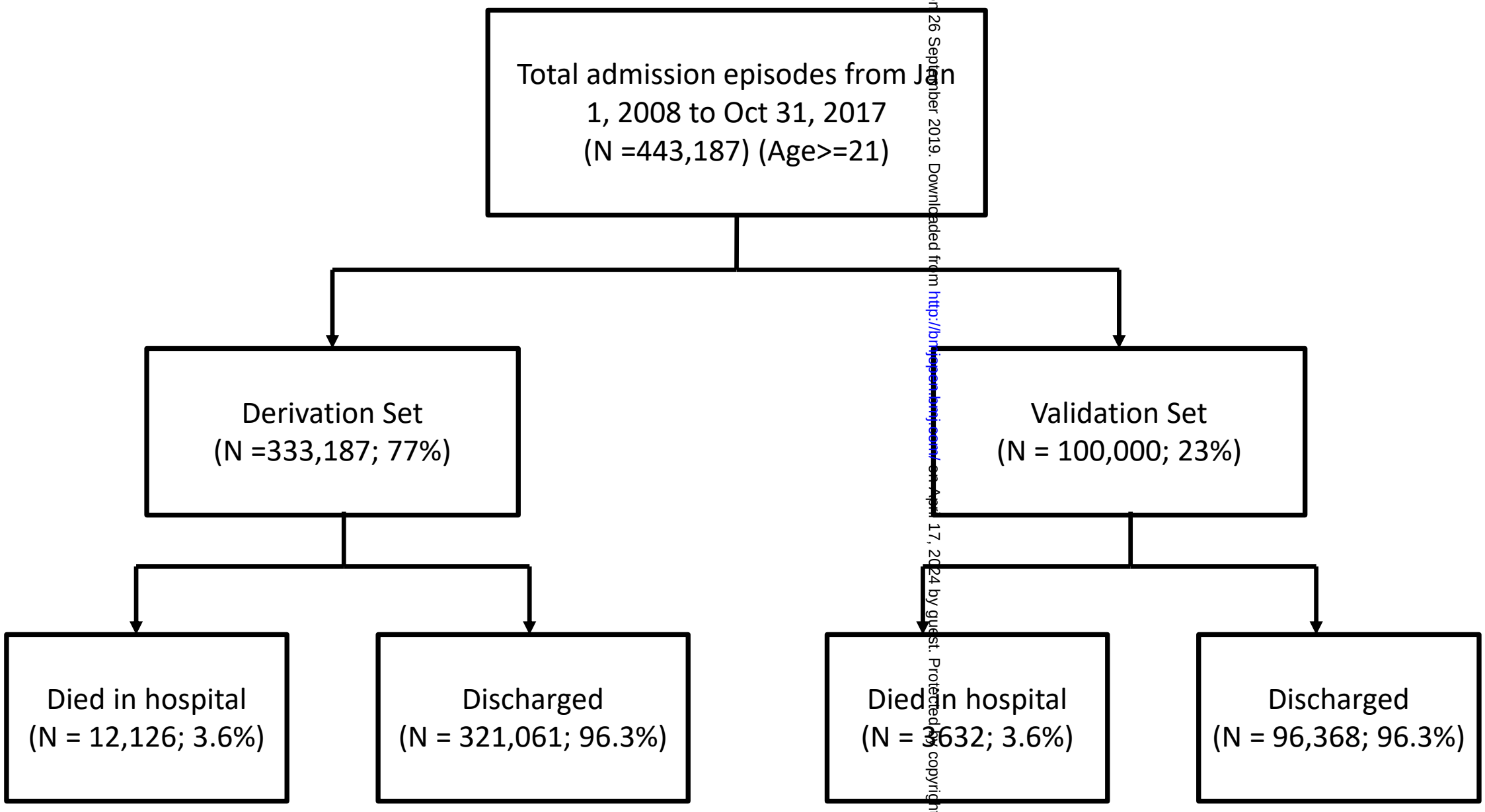

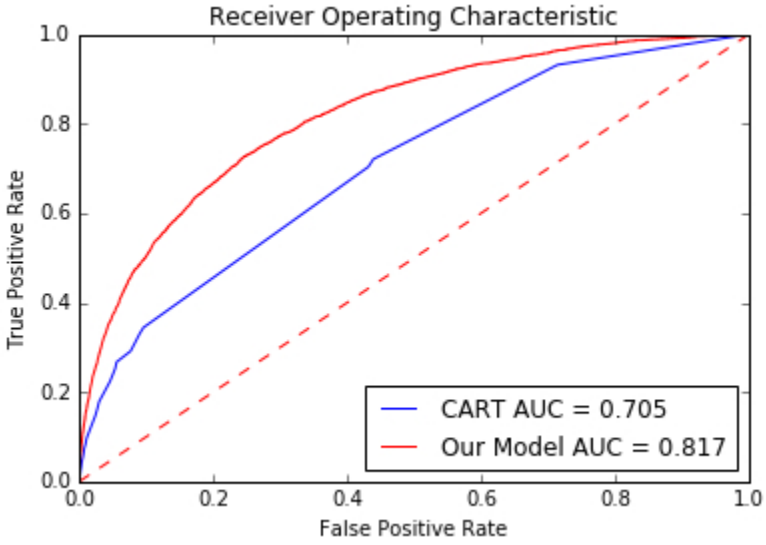

Figure 2: Receiver operating characteristic (ROC) curves of our model and CART score on the validation set.

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A Novel Model for Predicting Inpatient Mortality after Emergency Admission to Hospital in Singapore: A Retrospective Study

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A Novel Model for Predicting Inpatient Mortality after Emergency Admission to Hospital in Singapore: A Retrospective Study

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Abstract

Objectives: To identify risk factors for inpatient mortality after patients' emergency admission and create a novel model predicting inpatient mortality risk.

Design: This was a retrospective observational study using data extracted from the electronic health records (EHR). The data were randomly split into a derivation set and a validation set. The stepwise model selection was employed. We compared our model with one of the current clinical scores, Cardiac Arrest Risk Triage (CART) score.

Setting: A single tertiary hospital in Singapore.

Participants: All adult hospitalized patients, admitted via ED from Jan 1, 2008, to Oct 31, 2017 (n=433,187 by admission episodes)

Main outcome measure: The primary outcome of interest was inpatient mortality following this admission episode. The Area Under the Curve (AUC) of the operating characteristic curve (ROC) of the predictive model with sensitivity and specificity for optimized cut-offs.

Results: 15,758 (3.64%) of the episodes were observed inpatient mortality. 19 variables were observed as significant predictors and included in our final regression model. Our predictive model outperformed the CART score in terms of predictive power. The AUC of CART score and our final model was 0.705 (95% CI: 0.697-0.714) and 0.817 (95% CI: 0.810-0.824) respectively.

Conclusion: We developed and validated a model for inpatient mortality using EHR data collected in the ED. The performance of our model was more accurate than the CART score. Implementation of our model in the hospital can potentially predict imminent adverse events and institute appropriate clinical management.

Keywords: Inpatient mortality, emergency department (ED), predictive model, electronic health records (EHR)

Strengths and limitations of this study

- The study identified several risk factors and developed a novel model for predicting future risk of inpatient mortality based on features collected at ED.
- Large EHR database and high predictive power
- Single site study without external validation

Introduction

Inpatient mortality, a key performance indicator of health services, provides general information concerning patient care delivery. Despite decades of research, inpatient mortality remains an issue [1-3]. Lu et al. showed that preventable deaths in emergency admitted patients with early mortality are not rare[4]. The Harvard Medical Practice Study I estimated 27.6% of the adverse events as a result of negligence [5]. Even a delay of a few hours in transferring critically ill patients to the intensive care unit (ICU) results in increased mortality [6]. Several studies [7-9] have shown that physiological deterioration or abnormal vital signs before cardiac arrest or death were common, making it possible to predict the progression of adverse events. Previous intervention studies have demonstrated that inpatient mortality can be avoided by adequate care [10], frequent physiological measurement [11] or other necessary measures. However, few studies managed to model the risk factors related to inpatients mortality after patients' emergency admission through the emergency department (ED). Therefore, we proposed to utilize medical features collected at the ED to conduct predictive analysis, anticipating imminent adverse events and thus allowing physicians to respond appropriately.

There are numerous models for detecting mortality in the hospital, including the Early Warning Scores (EWS) system [12], which have been implemented in many hospitals to recognize early clinical deterioration. The concept of EWS was proposed by Morgan et al. in 1997 and it included mainly the vital signs variables such as heart rate, blood pressure, respiratory rate, temperature and neurological status [13]. Subsequently, multiple variants have been developed, such as NEWS [14], Modified EWS (MEWS) [15] and VitalPAC™ EWS (ViEWS) [16]. The adoption of EWS in the hospital was found to correlate with reduced mortality rates and improved overall patient outcomes in a systematic review [17]. However, several studies [18-20] pointed out its limitations such as over-sensitivity, low specificity, and the need for accompanying critical care outreach team. Accordingly, there still is a need for improvement in accurate recognition. In 2012, the Cardiac Arrest Risk Triage (CART) score [21] was developed with higher predictive power and usability than the MEWS. Furthermore, the increasing popularity of electronic health records (EHR) [22] creates an opportunity to acquire a more comprehensive and usable model for risk stratification in the hospital. Besides patient factors, non-patient factors including prolonged emergency boarding [23] , ED overcrowding [24] and day of week [25] were utilized to augment the model's sensitivity and specificity. Despite the common view of these worthwhile interventions, few clinical trials demonstrated a consistent improvement in reducing the hospital-wide mortality rate.

Currently, there are few studies on early risk stratification of ED patients for in-patient mortality in Singapore. A study in the United States [26] has focused on patients with a specific diagnosis. Increased age, low systolic blood pressure or sodium levels, elevated heart rate or creatinine at admission were identified as important predictors for inpatient mortality in patients hospitalized for heart failure. However, few studies report the general risk of inpatient mortality from the information gathered when patients are presented to the ED in Singapore. In this study, we aimed to derive and validate a mortality prediction model from the available information commonly collected in the ED, assisting doctors in identifying high-risk patients.

Methods

Study design and setting

We performed a retrospective, single-center study to derive a novel model to predict inpatient mortality in wards using routinely collected data in the ED and compared its accuracy to the CART score. Singapore is a city-state in Southeast Asia with 5.6 million people and diverse ethical composition. Its mixed healthcare system provides affordable care funded through both compulsory savings and partial subsidies. The site of this study is Singapore General Hospital (SGH), the largest and oldest tertiary hospital with more than 30 clinical disciplines and 1700 inpatient beds. Its ED receives over 120,000 visits and refers 36,000 inpatient admissions annually. EHR data was obtained from Singapore Health Services and employed in this study. This study was approved by Singapore Health Services' Centralized Institutional Review Board where patient consent was waived.

Patient and public involvement

Patients and the public were not involved in the design or planning of the study.

Study population and outcome

All patients visiting the ED from January 1, 2008 until October 31, 2017 who were subsequently admitted after their ED discharge across all clinical specialties in SGH were included in this study. We excluded patients who were below 21 years old and died in the ED. The primary outcome of interest was inpatient mortality, identified by the hospital's admission and discharge administrative database.

Data collection and variables

We extracted data from the hospital's EHR, named as the SingHealth Electronic Health lntelligence System (eHints). Patients' details were de-identified to ensure that the data were sufficiently anonymized. Death records were obtained from the national death registry and were matched to specific patients in the hospital. We selected variables that are available in the ED prior to hospital admission to ensure the model is clinically useful for early identification. Selected variables included four demographical variables, four ED administrative variables and eleven clinical variables. Demographic variables include age, gender, nationality, and race. ED administrative variables include consultation waiting time (unit: hour), ED boarding time (unit: hour), day of week, shift time. Among these, ED boarding time is the amount of time that patients spent from the first consultation to ED discharge. Consultation waiting time is the amount of time that patients spent from ED registration to the first consultation with ED physicians. Clinical variables include one clinical service variable, 6 commonly sampled vital signs and 4 commonly sampled laboratory tests; specifically, they are: blood gas (Yes/No), pulse (beats per minute), respiration rate (breaths per minute), fraction of inspired oxygen (FiO_2), blood oxygen saturation (SPO_2), diastolic blood pressure (mmHg), systolic blood pressure (mmHg), bicarbonate (mmol/L), creatinine (μmol/L), potassium (mmol/L), and sodium (mmol/L).

Statistical analysis

The data were analyzed using R version 3.42 (R Foundation, Vienna, Austria). After confirming the cohort, the data were randomly split into a derivation set (N =333,187; 77%) and a validation set (N=100,000; 23%). Derivation set was used to generate the

model. Model accuracy was reported on the validation set and bootstrapped samples were applied to calculate 95% confidence intervals (CIs). During this analysis, a value of vital signs or lab tests would be considered as an outlier if it were beyond the normal range on the basis of domain knowledge. All detected outliers were set to missing. Then, all missing values were imputed using the median value of the derivation dataset.

Baseline characteristics of the study population were analyzed on both derivation and validation sets to confirm similarity. In the descriptive summaries, frequencies and percentage were reported for categorical variables, while means and standard deviations (SDs) were reported for continuous variables. We compared admitted patients with and without inpatient mortality using two-tailed Student's t-test for continuous variables and chi-square test for categorical variables. The p-value shows the significance of difference for admitted patients between inpatient mortality and successful discharge. Because of the large sample size associated with EHRs, the threshold for declaring statistical significance level was set at $p<0.01$, much smaller than the usual 0.05 level, in order to reduce the chances of finding spurious effects.

The prediction model was built by applying two-step logistic regression to the derivation set. Firstly, univariate analysis was performed on all variables to access their independent association to inpatient mortality. The largest cohort of each variable was selected as the baseline for comparison with other groups. Odds ratios (OR) and the corresponding CI were calculated. Secondly, variables with $p<0.01$ from the first step were selected to be analyzed using multivariate logistic regression with backward stepwise variable selection.

In the final regression model, the modeling performance was evaluated on the validation set. Our model generated a probability of inpatient mortality from 0 to 1 for each admission episodes. The predictive power of the model was calculated using the area under the curve (AUC) in the receiver operating characteristic (ROC) analysis. In order to compare our model with current clinical scores, we also applied Cardiac Arrest Risk Triage (CART) [21] score into the same validation set and compared the performance between CART score and our novel model.

Results

Basic characteristics

A total of 433,187 unique emergency admission episodes were included in this study. Of the 433,187 eligible episodes, 15,758 episodes (3.64%) met the outcome, i.e. inpatient mortality. The mean age of the whole cohort was 62.1 (SD=17.7) years, 50.1% were female (n=216,914), most patients were Singaporean (90.5%, n=392,219), the ethnic compositions were similar to population norms (71.2% for Chinese,12.1% for Malay, 10.6% for Indian and 6.1% for others), 2.1% (n=9144) of the patients received blood gas services in the ED, the mean ED boarding time was 4.78 (SD=3.83) hours and the mean ED consultation waiting time was 0.77 (SD=0.79) hours).

The whole cohort was subsequently divided into the derivation and validation set as displayed in Figure 1. Table 1 shows the statistics of highly similar population in both sets. The derivation set was constitutive of patients with a mean age of 62.1 (SD=17.7), with similar male (49.9%) and female (50.1%) proportion, with the ethnic

breakdown representing the general Singaporean population. Compared to the patients who survived to discharge, patients who died in hospital were older, had shorter ED boarding time and consultation waiting time, and a higher probability of receiving blood gas services while in the ED. They also had lower SPO_2, blood pressure, bicarbonate, and sodium concentration with a higher pulse, respiration rate, FiO_2, and potassium and creatinine concentration.

Univariable Analysis

Table 2 shows the OR and adjusted OR of all demographic, administrative and clinical variables. All variables were respectively significant in the univariate regression in terms of the p-value. We treated vital signs and lab test values as continuous variables and their odds ratios represent the increase or decrease in the odds of inpatient mortality for a one-unit increase in this feature. Observed from the demographical data, patients who were male, Chinese ethnic Singaporean had a higher risk of inpatient mortality. Patients who were foreigners and other races beyond Chinese were unlikely to die in the hospital after emergency admission. Administratively, patients who had shorter consultation waiting time and ED boarding time were more likely to die in hospital. Clinically, patients with a higher pulse, respiration rate, FIO_2, creatinine and potassium concentration and lower blood pressure, SPO_2, bicarbonate, and sodium concentration had a higher risk of inpatient death. All 19 variables were selected for multivariate stepwise analysis as a result of their p-values all below 0.01.

Multivariable Analysis

All variables were used to create the stepwise regression model and no variable was removed through stepwise variable selection. The final model contains 19 variables and the multivariate analysis with the corresponding adjusted odds ratio are shown in Table 2. Older Singaporean with Chinese ethnic had a higher change of inpatient mortality. Although diastolic blood pressure, shift time and day of week were not very significant in multivariate analysis, they were included into the final model after backward stepwise variable selection and due to the clinical judgments [27].

Predictive Model Performance

Our model shows good discriminatory capability on predicting inpatient mortality. On the validation set, the model achieved the AUC of 0.817 (95% CI: 0.810-0.824) with a sensitivity of 73.1% (95% CI: 70.7%-77.6%) and a specificity of 75.4% (95% CI: 70.9%-76.9%) under the optimal threshold (Probability = 0.037) as shown in Figure 2. In contrast, the performance of the existing CART score achieved the AUC of 0.705 (95% CI: 0.697-0.714) with the sensitivity of 72.1% (95% CI: 70.7%-73.6%) and specificity of 56.1% (95% CI: 55.8%-56.4%) under the optimal threshold (CART value = 7). The calibration curve of our developed model is shown in Figure 3.

Discussion

In this study, the main finding is that 19 routinely collected variables from the ED EHR system can be utilized to predict inpatient mortality for the patients after their emergency admission. Our predictive model has better discriminative power than the CART score (AUC, 0.817 vs. 0.705) on the same validation set. The results suggest the possibility of building a reliable inpatient mortality model from the basic demographic, administrative and limited clinical information acquired in the ED when

patients are admitted into the hospital through ED. By deriving a model of inpatient mortality using routinely collected ED data, our study identifies factors associated with inpatient mortality and provides a potentially useful tool for risk stratification of ED patients.

A major strength of our model is the size of the dataset, which was used for deriving this model. This is among the largest datasets used to generate an inpatient mortality predictive model with a cohort of over 430,000 patients in a 10-year period, targeting almost the whole hospital. In addition, it included a large amount of diversity due to Singapore's diverse population. Another advantage of our model is its comprehensiveness, making it applicable to the general patient population presenting to the ED rather than some specific patient subgroups. Furthermore, the application of EHR systems will make our model easy to implement.

There are several reasons why the CART score underperformed our novel model in our study. At first, the CART score did not comprise laboratory test variables. The importance of including routine laboratory test values in the risk predictive model has been demonstrated in other studies. For example, in a study [28] by Churpek and colleagues, including laboratory values in his model contributes important knowledge to the field. Pine et al. [29] and Froom et al. [30] also gave evidence of laboratory values improving predictions of hospital mortality. Secondly, CART was unable to make use of valuable routine administrative data. Guttmann et al. [31] and Parker et al. [32] have previously shown that waiting time, work shifts and other administrative variables were greatly associated with inpatient mortality and hospital admission. In comparison, our model takes both ED administrative data and laboratory test value into account, proving a higher accuracy than the CART score.

Previous researchers have created several predictive tools for inpatient mortality. For example, Prytherch et al. [16] developed the ViEWS score, mainly utilizing vital signs variables to predict mortality for hospitalized patients within 24 hours. The significant predictors of mortality were the pulse, breathing rate, temperature, systolic BP, SPO_2, FiO_2 and mental status. Although vital signs are potential predictors of adverse events, it gives rapid response team (RRT) too short time to respond, especially in a hospital with full capacity or lack of manpower. Since changes in vital signs occur hours before the event, these changes may not be seen at the time of consultation at the ED when potentially high-risk patients have non-discriminatory vital signs similar to that of other healthy patients. Secondly, elderly patients may not have the expected vital signs changes associated with the clinical deterioration and modeling using vital signs alone might miss out cases. It was demonstrated in a study [33] of Churpek and colleagues, who suggests additional predictors of adverse events for elderly patients. Our model is notably different from this because it involved laboratory test values and administrative data besides vital signs and were presumably appropriate for the rapidly aging population in Singapore [34].

Another study [35] in Australia employed multivariable logistic regression of variables from datasets obtained at triage in one hospital to derive and validate a mortality prediction model, Triage Information Mortality Model (TIMM). This TIMM included age, gender, time of year, ambulance, Australasian triage scale and nine chief complaint codes. However, it did not include any physiological variables that were considered as strong predictors and could be obtained conveniently from the EHR

system. In comparison, our model combined demographic, administrative, and physiological variables, which will provide a much more comprehensive profile and capture the sufficient information of the patients in the ED, hence improving the model's predictive power.

Our data analysis also produces some notable findings regarding risk factors related to inpatient mortality. It identified increased age, low blood pressure, high heart rate and elevated creatinine and potassium concentration and decreased sodium and bicarbonate concentration when patients are present to ED as important predictors for inpatient mortality. Besides these factors, our study identified some non-patient factors such as emergency boarding time, day of week and shift time, which can affect patient outcomes. Presenting to ED on Friday or weekend and shift time 24:00 to 8:00 were found to increases risk, consistent with a large study of Aylin and colleagues[36] in the US, which shows 10% higher odds of death for all emergency admission at the weekend compared with admission during a weekday. An excess in mortality may reflect differences in quality of care, potentially as a result of the ED overcrowding, insufficient services, change of shift and slower access to critical investigations. However, the differences in mortality decreased after adjustment for other factors in our analysis Shorter ED boarding time and consultation waiting time become predictors potentially due to severely critical patients with a fast track to admission and intensive resources.

The information needed for this novel model is readily available at the time of consultation at the ED when the first set of laboratory tests are done. When a physician has to make a decision on further management and disposition of the patient. Our model can be deployed for early identification of high-risk patients. Afterward, we can allocate more intensive resources to high-risk patients with a sufficient level of monitoring, increasing nursing attention [37], activation of a rapid response team [38] or medical emergency team (MET) [39]. Thus, through our model, these patients could be seen early after emergency admission and above interventions can be started to avoid severe sudden adverse events during their inpatient stay. Similarly, low-risk patients below the predictive threshold could potentially be safely identified who might not need admission or intensive monitoring and thus save precious in-patient resources. Overall, the good performance, usability and widespread adoption of advanced EHR system make our model easy to integrate into the hospital electronic system such that the probability of inpatient mortality or real-time risk score can be calculated for every patient when they are presented to the ED and ready for admission to hospital. The model can supplement the physician's judgment in decision-making.

Limitation

There are several limitations in this study. First, all variables included in this study are based on EHR and it only contains routinely collected information and does not include all information available that should, in theory, be elicited early when patients are present to the ED. For example, comorbidity information or Carlson indexes[40] was considered as significant predictors. However, they were not available in our current analysis. Other health utilizations such as intubation and resuscitation have been proved predictive of overall mortality and should have been included in our model. Furthermore, due to the lack of neurological features (GCS score), which were not common feature collected in Singapore hospital. Thus, we were not able to calculate

the MEWS score and compare it with our model. Second, this is a single-site study at a tertiary hospital and our findings may not be generalized to other settings and thus, our results need to be validated in different hospital settings in Singapore or other countries in the future research, especially population consisting of different ethnicities to avoid center-specific bias. Prospective data collection is supposed to explore the clinical value and effect of our model in practice and further prove its efficacy. Third, our model is complex and the calculation should be done electronically. The ability to implement an EHR system varies in a different hospital and lack of features monitored by the system may limit the generalizability of our model.

Conclusion

In summary, we identified several risk factors and developed a novel model for inpatient mortality using 10-year EHR data routinely collected at the ED. The discriminative capability of our model was better than that of the traditional clinical score, CART score. Implementation of our model in the ED can allow accurate and timely identification of a high-risk cohort for interventions during their inpatient stay, resulting in a potential reduction in avoidable inpatient mortality.

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Table 1: Description of the study cohort

	Derivation Set				Validation Set			
	All Admission Episodes (n=333,187)	Discharged (n=321,061)	Inpatient Mortality (n=12,126)	p-Value	All Admission Episodes (n=100,000)	Discharged (n=96,368)	Inpatient Mortality (n=3,632)	p-Value
Demographics								
Age (SD)	62.12 (17.67)	61.79 (17.71)	70.78 (13.92)	<0.001	62.12 (17.65)	61.79 (17.69)	70.86 (13.84)	<0.001
Gender (%)				<0.001				<0.001
Male	166354 (49.9)	159742 (49.8)	6612 (54.5)		49892 (49.9)	47902 (49.7)	1990 (54.8)	
Female	166833(50.1)	161319(50.2)	5514(45.5)		50108(50.1)	48466(50.3)	1642(45.2)	
Nationality (%)				<0.001				<0.001
Singaporean	301661(90.5)	290204(90.4)	11457(94.5)		90558(90.6)	87102(90.4)	3456(95.2)	
Foreigner	31526 (9.5)	30857 (9.6)	669 (5.5)		9442 (9.4)	9266 (9.6)	176 (4.8)	
Race (%)				<0.001				<0.001
Chinese	237147 (71.2)	227418 (70.8)	9729 (80.2)		71196 (71.2)	68242 (70.8)	2954 (81.3)	
Malay	40377 (12.1)	39210 (12.2)	1167 (9.6)		12171 (12.2)	11815 (12.3)	356 (9.8)	
Indian	35259 (10.6)	34466 (10.7)	793 (6.5)		10585 (10.6)	10348 (10.7)	237 (6.5)	
Others	20404 (6.1)	19967 (6.2)	437 (3.6)		6048 (6.0)	5963 (6.2)	85 (2.3)	
ED Administrative Data								
Consultation waiting time (SD)	0.77 (0.80)	0.78 (0.80)	0.48 (0.58)	<0.001	0.77 (0.79)	0.78 (0.79)	0.48 (0.57)	<0.001
ED boarding time (SD)	4.78 (3.83)	4.80 (3.83)	4.35 (3.70)	<0.001	4.78 (3.84)	4.80 (3.84)	4.40 (3.94)	<0.001
Day of week (%)				<0.001				0.002
Midweek	144866 (43.5)	139817 (43.5)	5049 (41.6)		43395 (43.4)	41897 (43.5)	1498 (41.2)	
Monday	55643 (16.7)	53726 (16.7)	1917 (15.8)		16659 (16.7)	16088 (16.7)	571 (15.7)	
Friday	46724 (14.0)	44932 (14.0)	1792 (14.8)		13915 (13.9)	13380 (13.9)	535 (14.7)	
Weekend	85954 (25.8)	82586 (25.7)	3368 (27.8)		26031 (26.0)	25003 (25.9)	1028 (28.3)	
Shift time (%)				0.002				0.243
08:00 to 16:00	167802 (50.4)	161871 (50.4)	5931 (48.9)		50514 (50.5)	48729 (50.6)	1785 (49.1)	

16:00 to 24:00	125745 (37.7)	121075 (37.7)	4670 (38.5)		37896 (37.9)	36480 (37.9)	1416 (39.0)	
24:00 to 8:00	39640 (11.9)	38115 (11.9)	1525 (12.6)		11590 (11.6)	11159 (11.6)	431 (11.9)	
Clinical Data								
Blood gas (%)	6971 (2.1)	6047 (1.9)	924 (7.6)	<0.001	2173 (2.2)	1889 (2.0)	284 (7.8)	<0.001
Pulse (SD)	82.70 (17.02)	82.28 (16.69)	93.85 (21.32)	<0.001	82.71 (16.98)	82.32 (16.66)	93.21 (21.44)	<0.001
Respiration rate (SD)	17.85 (1.74)	17.81 (1.63)	18.81 (3.40)	<0.001	17.84 (1.73)	17.81 (1.63)	18.78 (3.36)	<0.001
FiO_2 (SD)	23.10 (10.14)	22.63 (8.50)	35.43 (27.44)	<0.001	23.07 (10.02)	22.64 (8.46)	34.67 (26.89)	<0.001
SPO_2 (SD)	97.99 (3.18)	98.02 (3.05)	97.14 (5.60)	<0.001	97.98 (3.23)	98.01 (3.07)	97.14 (5.97)	<0.001
Diastolic BP (SD)	71.34 (13.46)	71.49 (13.33)	67.22 (15.81)	<0.001	71.39 (13.55)	71.57 (13.42)	66.65 (15.88)	<0.001
Systolic BP (SD)	133.76 (25.33)	134.12 (25.17)	124.29 (27.58)	<0.001	133.87 (25.44)	134.27 (25.25)	123.16 (27.87)	<0.001
Bicarbonate (SD)	22.80 (3.54)	22.86 (3.43)	21.18 (5.48)	<0.001	22.79 (3.55)	22.85 (3.44)	21.23 (5.44)	<0.001
Creatinine (SD)	146.60 (197.88)	144.91 (197.04)	191.47 (214.24)	<0.001	145.86 (196.34)	144.36 (195.53)	185.80 (212.89)	<0.001
Potassium (SD)	4.16 (0.67)	4.15 (0.66)	4.38 (0.92)	<0.001	4.16 (0.68)	4.15 (0.66)	4.35 (0.89)	<0.001
Sodium (SD)	135.11 (4.85)	135.18 (4.73)	133.29 (7.26)	<0.001	135.12 (4.86)	135.19 (4.72)	133.20 (7.43)	<0.001

ED=Emergency Department, SD= Standard Deviation, ED=Emergency Department, SD= Standard Deviation, BP=Blood Pressure, FiO_2= Fraction of inspired oxygen, SpO_2= Blood Oxygen Saturation

Table 2: Univariable and multivariable analysis

	Unadjusted OR (95% CI)	p-Value	Adjusted OR (95% CI)	Adjusted p-Value
Demographics				
Age	1.034(1.033-1.035)	<0.001	1.035(1.033-1.036)	<0.001
Gender				
Female	Baseline		Baseline	
Male	1.211(1.168-1.256)	<0.001	1.144(1.1-1.19)	<0.001
Nationality				
Singaporean	Baseline		Baseline	
Foreigner	0.549(0.508-0.594)	<0.001	0.898(0.82-0.984)	0.021
Race				
Chinese	Baseline		Baseline	
Malay	0.696(0.654-0.74)	<0.001	0.865(0.809-0.925)	<0.001
Indian	0.538(0.5-0.579)	<0.001	0.69(0.638-0.746)	<0.001
Others	0.512(0.464-0.564)	<0.001	0.773(0.692-0.862)	<0.001
ED Administrative				
Consultation waiting time	0.437(0.42-0.454)	<0.001	0.683(0.659-0.709)	<0.001
ED boarding time	0.96(0.954-0.966)	<0.001	0.981(0.975-0.987)	<0.001
Day of Week				
Midweek	Baseline		Baseline	
Monday	0.988(0.937-1.042)	0.661	1.009(0.953-1.068)	0.761
Friday	1.104(1.045-1.167)	<0.001	1.084(1.022-1.149)	0.007
Weekend	1.129(1.08-1.181)	<0.001	1.001(0.954-1.051)	0.954
Shift time				
8:00 to 16:00	Baseline		Baseline	
16:00 to 24:00	1.053(1.012-1.095)	0.01	1.023(0.981-1.067)	0.288
24:00 to 8:00	1.092(1.031-1.156)	0.003	0.94(0.883-1)	0.05
Clinical Data				
Blood gas (Yes=1, No=0)	4.297(4-4.617)	<0.001	1.224(1.121-1.336)	<0.001
Pulse	1.035(1.034-1.036)	<0.001	1.025(1.024-1.026)	<0.001
Respiration rate	1.2(1.192-1.208)	<0.001	1.034(1.027-1.042)	<0.001
FiO_2	1.04(1.039-1.04)	<0.001	1.028(1.027-1.029)	<0.001
SPO_2	0.966(0.963-0.969)	<0.001	0.979(0.976-0.983)	<0.001
Diastolic BP	0.975(0.973-0.976)	<0.001	0.999(0.997-1.001)	0.18
Systolic BP	0.984(0.983-0.984)	<0.001	0.985(0.984-0.986)	<0.001
Bicarbonate	0.889(0.885-0.893)	<0.001	0.967(0.962-0.972)	<0.001
Creatinine	1.001(1.001-1.001)	<0.001	1.001(1.001-1.001)	<0.001
Potassium	1.528(1.494-1.562)	<0.001	1.159(1.129-1.189)	<0.001
Sodium	0.938(0.935-0.941)	<0.001	0.961(0.958-0.964)	<0.001

ED=Emergency Department, SD= Standard Deviation, BP=Blood Pressure, OR=Odd Ratio, FiO_2= Fraction of inspired oxygen, SpO_2= Blood Oxygen Saturation

Author Contributions

FX, NL and MEHO conceived and designed the study. NL, MEHO and BC supervised the study. FX and SXW performed data retrieval and preprocessing. FX analyzed the data. FX, NL, YA, LLL, AFWH, SSWL, DBM, MEHO and BC interpreted the results. FX wrote the first draft of the paper and all authors critically revised the paper and gave final approval for publication.

Competing interests: None declared

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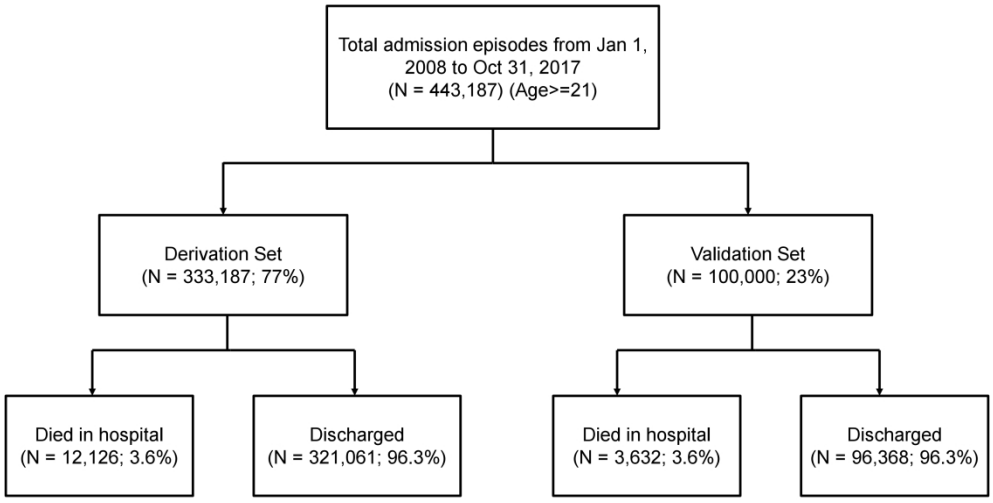
Ethics approval:
This study was approved by Singapore Health Services (SingHealth) Centralized Institutional Review Board (CIRB Ref 2017/2666) with a waiver of informed consent.

Provenance and peer review: Not commissioned; externally peer reviewed.

Data sharing statement: Details of the variables and derived predictive model are available from the corresponding author.

Word count: 3360



Flow of patients' emergency admissions.

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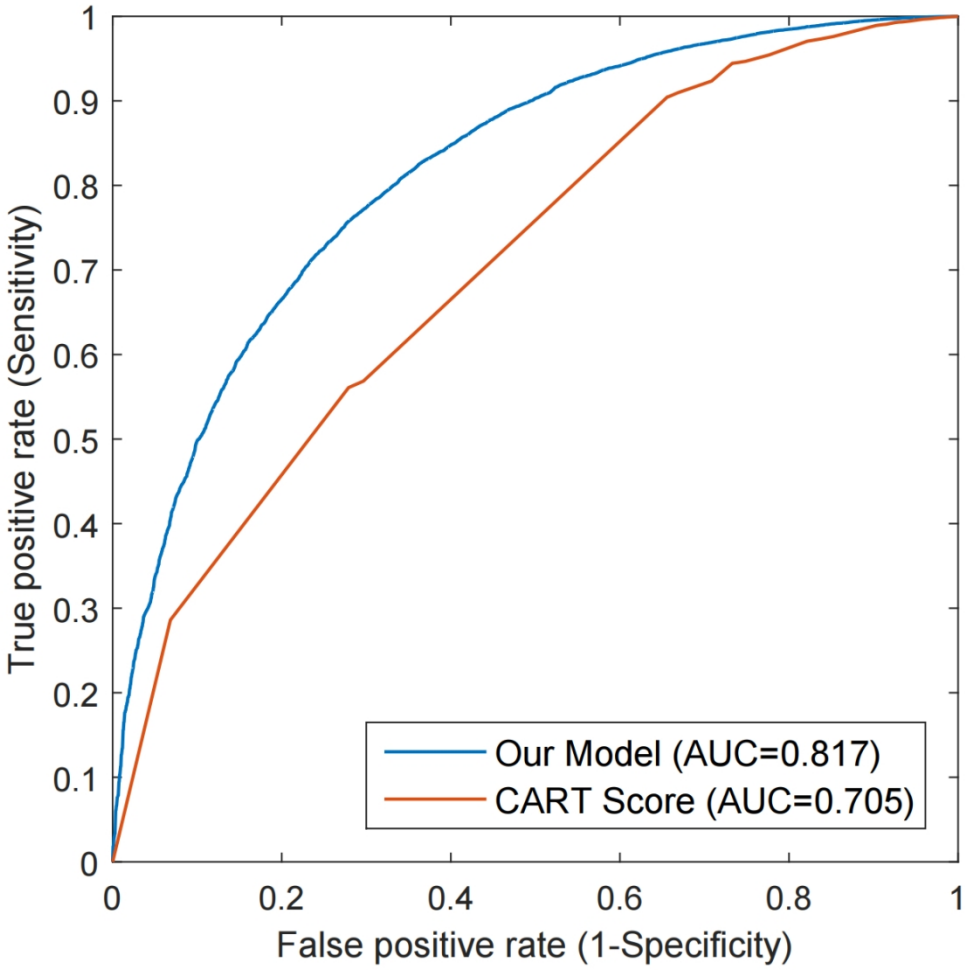

Receiver operating characteristic (ROC) curves of our model and CART score on the validation set.

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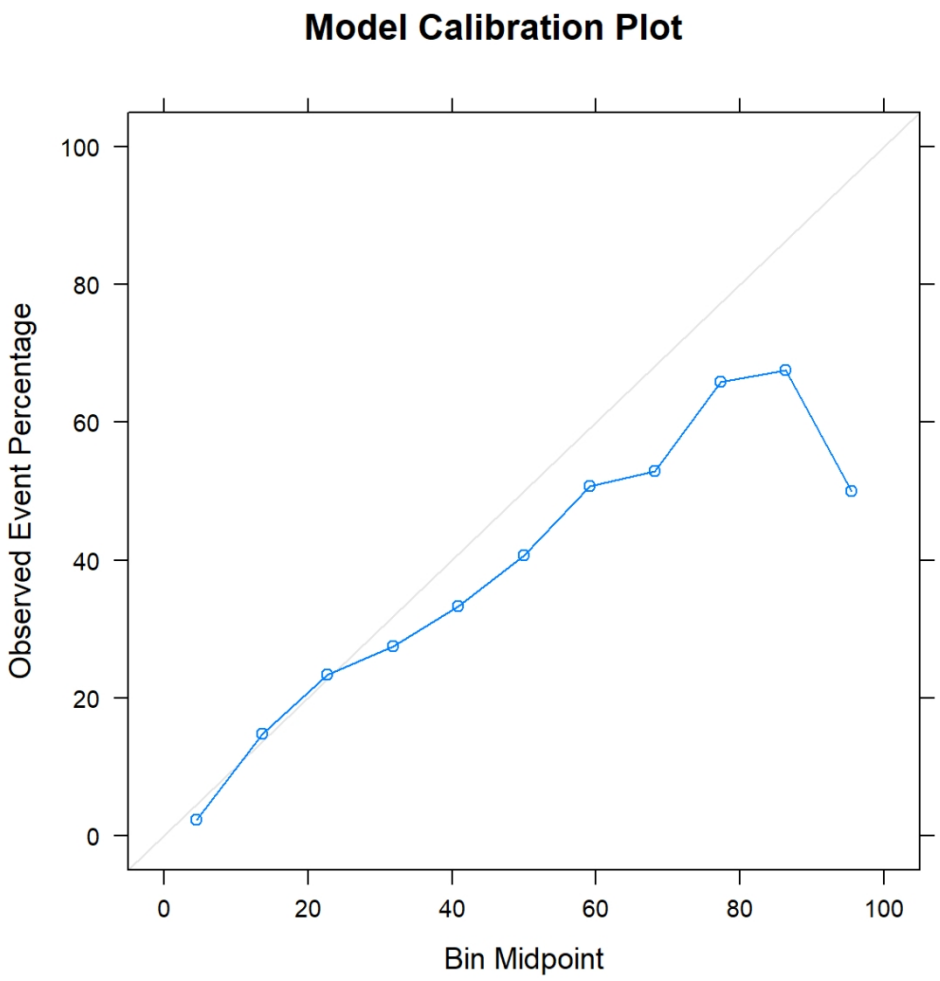

Model calibration curve on the validation set.

141x141mm (216 x 216 DPI)

TRIPOD Checklist: Prediction Model Development and Validation

Section/Topic	Item		Checklist Item	Page
Title and abstract				
Title	1	D;V	Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted.	1
Abstract	2	D;V	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.	1-2
Introduction				
Background and objectives	3a	D;V	Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models.	3
	3b	D;V	Specify the objectives, including whether the study describes the development or validation of the model or both.	3
Methods				
Source of data	4a	D;V	Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable.	4
	4b	D;V	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.	
Participants	5a	D;V	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres.	4
	5b	D;V	Describe eligibility criteria for participants.	4
	5c	D;V	Give details of treatments received, if relevant.	
Outcome	6a	D;V	Clearly define the outcome that is predicted by the prediction model, including how and when assessed.	4
	6b	D;V	Report any actions to blind assessment of the outcome to be predicted.	
Predictors	7a	D;V	Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured.	4
	7b	D;V	Report any actions to blind assessment of predictors for the outcome and other predictors.	
Sample size	8	D;V	Explain how the study size was arrived at.	5
Missing data	9	D;V	Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.	5
Statistical analysis methods	10a	D	Describe how predictors were handled in the analyses.	4-5
	10b	D	Specify type of model, all model-building procedures (including any predictor selection), and method for internal validation.	4-5
	10c	V	For validation, describe how the predictions were calculated.	5
	10d	D;V	Specify all measures used to assess model performance and, if relevant, to compare multiple models.	5
	10e	V	Describe any model updating (e.g., recalibration) arising from the validation, if done.	6
Risk groups	11	D;V	Provide details on how risk groups were created, if done.	
Development vs. validation	12	V	For validation, identify any differences from the development data in setting, eligibility criteria, outcome, and predictors.	5
Results				
Participants	13a	D;V	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.	5
	13b	D;V	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.	5
	13c	V	For validation, show a comparison with the development data of the distribution of important variables (demographics, predictors and outcome).	5
Model development	14a	D	Specify the number of participants and outcome events in each analysis.	5
	14b	D	If done, report the unadjusted association between each candidate predictor and outcome.	6
Model specification	15a	D	Present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point).	6
	15b	D	Explain how to the use the prediction model.	8
Model performance	16	D;V	Report performance measures (with CIs) for the prediction model.	6
Model-updating	17	V	If done, report the results from any model updating (i.e., model specification, model performance).	
Discussion				
Limitations	18	D;V	Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).	8-9
Interpretation	19a	V	For validation, discuss the results with reference to performance in the development data, and any other validation data.	7-8
	19b	D;V	Give an overall interpretation of the results, considering objectives, limitations, results from similar studies, and other relevant evidence.	6-8
Implications	20	D;V	Discuss the potential clinical use of the model and implications for future research.	8
Other information				
Supplementary information	21	D;V	Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets.	
Funding	22	D;V	Give the source of funding and the role of the funders for the present study.	16

*Items relevant only to the development of a prediction model are denoted by D, items relating solely to a validation of a prediction model are denoted by V, and items relating to both are denoted D;V. We recommend using the TRIPOD Checklist in conjunction with the TRIPOD Explanation and Elaboration document.

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A Novel Model for Predicting Inpatient Mortality after Emergency Admission to Hospital in Singapore: A Retrospective Observational Study

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Abstract

Objectives: To identify risk factors for inpatient mortality after patients' emergency admission and create a novel model predicting inpatient mortality risk.

Design: This was a retrospective observational study using data extracted from the electronic health records (EHR). The data were randomly split into a derivation set and a validation set. The stepwise model selection was employed. We compared our model with one of the current clinical scores, Cardiac Arrest Risk Triage (CART) score.

Setting: A single tertiary hospital in Singapore.

Participants: All adult hospitalized patients, admitted via ED from Jan 1, 2008, to Oct 31, 2017 (n=433,187 by admission episodes)

Main outcome measure: The primary outcome of interest was inpatient mortality following this admission episode. The area under the curve (AUC) of the receiver operating characteristic (ROC) curve of the predictive model with sensitivity and specificity for optimized cut-offs.

Results: 15,758 (3.64%) of the episodes were observed inpatient mortality. 19 variables were observed as significant predictors and included in our final regression model. Our predictive model outperformed the CART score in terms of predictive power. The AUC of CART score and our final model was 0.705 (95% CI: 0.697-0.714) and 0.817 (95% CI: 0.810-0.824) respectively.

Conclusion: We developed and validated a model for inpatient mortality using EHR data collected in the ED. The performance of our model was more accurate than the CART score. Implementation of our model in the hospital can potentially predict imminent adverse events and institute appropriate clinical management.

Keywords: Inpatient mortality, emergency department (ED), predictive model, electronic health records (EHR)

Strengths and limitations of this study

- The study identified several risk factors and developed a novel model for predicting future risk of inpatient mortality based on features collected at ED.
- Large EHR database and high predictive power
- Single site study without external validation

Introduction

Inpatient mortality, a key performance indicator of health services, provides general information concerning patient care delivery. Despite decades of research, inpatient mortality remains an issue [1-3]. Lu et al. showed that preventable deaths in emergency admitted patients with early mortality are not rare[4]. The Harvard Medical Practice Study I estimated 27.6% of the adverse events as a result of negligence [5]. Even a delay of a few hours in transferring critically ill patients to the intensive care unit (ICU) results in increased mortality [6]. Several studies [7-9] have shown that physiological deterioration or abnormal vital signs before cardiac arrest or death were common, making it possible to predict the progression of adverse events. Previous intervention studies have demonstrated that inpatient mortality can be avoided by adequate care [10], frequent physiological measurement [11] or other necessary measures. However, few studies managed to model the risk factors related to inpatients mortality after patients' emergency admission through the emergency department (ED). Therefore, we proposed to utilize medical features collected at the ED to conduct predictive analysis, anticipating imminent adverse events and thus allowing physicians to respond appropriately.

There are numerous models for detecting mortality in the hospital, including the Early Warning Scores (EWS) system [12], which have been implemented in many hospitals to recognize early clinical deterioration. The concept of EWS was proposed by Morgan et al. in 1997 and it included mainly the vital signs variables such as heart rate, blood pressure, respiratory rate, temperature and neurological status [13]. Subsequently, multiple variants have been developed, such as NEWS [14], Modified EWS (MEWS) [15] and VitalPAC™ EWS (ViEWS) [16]. The adoption of EWS in the hospital was found to correlate with reduced mortality rates and improved overall patient outcomes in a systematic review [17]. However, several studies [18-20] pointed out its limitations such as over-sensitivity, low specificity, and the need for accompanying critical care outreach team. Accordingly, there still is a need for improvement in accurate recognition. In 2012, the Cardiac Arrest Risk Triage (CART) score [21] was developed with higher predictive power and usability than the MEWS. Furthermore, the increasing popularity of electronic health records (EHR) [22] creates an opportunity to acquire a more comprehensive and usable model for risk stratification in the hospital. Besides patient factors, non-patient factors including prolonged emergency boarding [23], ED overcrowding [24] and day of week [25] were utilized to augment the model's sensitivity and specificity. Despite the common view of these worthwhile interventions, few clinical trials demonstrated a consistent improvement in reducing the hospital-wide mortality rate.

Currently, there are few studies on early risk stratification of ED patients for in-patient mortality in Singapore. A study in the United States [26] has focused on patients with a specific diagnosis. Increased age, low systolic blood pressure or sodium levels, elevated heart rate or creatinine at admission were identified as important predictors for inpatient mortality in patients hospitalized for heart failure. However, few studies report the general risk of inpatient mortality from the information gathered when patients are presented to the ED in Singapore. In this study, we aimed to derive and validate a mortality prediction model from the available information commonly collected in the ED, assisting doctors in identifying high-risk patients.

Methods

Study design and setting

We performed a retrospective, single-center study to derive a novel model to predict inpatient mortality in wards using routinely collected data in the ED and compared its accuracy to the CART score. Singapore is a city-state in Southeast Asia with 5.6 million people and diverse ethical composition. Its mixed healthcare system provides affordable care funded through both compulsory savings and partial subsidies. The site of this study is Singapore General Hospital (SGH), the largest and oldest tertiary hospital with more than 30 clinical disciplines and 1700 inpatient beds. Its ED receives over 120,000 visits and refers 36,000 inpatient admissions annually. EHR data was obtained from Singapore Health Services and employed in this study. This study was approved by Singapore Health Services' Centralized Institutional Review Board where patient consent was waived.

Patient and public involvement

Patients and the public were not involved in the design or planning of the study.

Study population and outcome

All patients visiting the ED from January 1, 2008 until October 31, 2017 who were subsequently admitted after their ED discharge across all clinical specialties in SGH were included in this study. We excluded patients who were below 21 years old and died in the ED. The primary outcome of interest was inpatient mortality, identified by the hospital's admission and discharge administrative database.

Data collection and variables

We extracted data from the hospital's EHR, named as the SingHealth Electronic Health lntelligence System (eHints). Patients' details were de-identified to ensure that the data were sufficiently anonymized. Death records were obtained from the national death registry and were matched to specific patients in the hospital. We selected variables that are available in the ED prior to hospital admission to ensure the model is clinically useful for early identification. Selected variables included four demographical variables, four ED administrative variables and eleven clinical variables. Demographic variables include age, gender, nationality, and race. ED administrative variables include consultation waiting time (unit: hour), ED boarding time (unit: hour), day of week, shift time. Among these, ED boarding time is the amount of time that patients spent from the first consultation to ED discharge. Consultation waiting time is the amount of time that patients spent from ED registration to the first consultation with ED physicians. Clinical variables include one clinical service variable, 6 commonly sampled vital signs and 4 commonly sampled laboratory tests; specifically, they are: blood gas (Yes/No), pulse (beats per minute), respiration rate (breaths per minute), fraction of inspired oxygen (FiO_2), blood oxygen saturation (SPO_2), diastolic blood pressure (mmHg), systolic blood pressure (mmHg), bicarbonate (mmol/L), creatinine (μmol/L), potassium (mmol/L), and sodium (mmol/L).

Statistical analysis

The data were analyzed using R version 3.42 (R Foundation, Vienna, Austria). After confirming the cohort, the data were randomly split into a derivation set (N =333,187; 77%) and a validation set (N=100,000; 23%). Derivation set was used to generate the

model. Model accuracy was reported on the validation set and bootstrapped samples were applied to calculate 95% confidence intervals (CIs). During this analysis, a value of vital signs or lab tests would be considered as an outlier if it were beyond the normal range on the basis of domain knowledge. All detected outliers were set to missing. Then, all missing values were imputed using the median value of the derivation dataset.

Baseline characteristics of the study population were analyzed on both derivation and validation sets to confirm similarity. In the descriptive summaries, frequencies and percentage were reported for categorical variables, while means and standard deviations (SDs) were reported for continuous variables. We compared admitted patients with and without inpatient mortality using two-tailed Student's t-test for continuous variables and chi-square test for categorical variables. The p-value shows the significance of difference for admitted patients between inpatient mortality and successful discharge. Because of the large sample size associated with EHRs, the threshold for declaring statistical significance level was set at $p<0.01$, much smaller than the usual 0.05 level, in order to reduce the chances of finding spurious effects.

The prediction model was built by applying two-step logistic regression to the derivation set. Firstly, univariate analysis was performed on all variables to access their independent association to inpatient mortality. The largest cohort of each variable was selected as the baseline for comparison with other groups. Odds ratios (OR) and the corresponding CI were calculated. Secondly, variables with $p<0.01$ from the first step were selected to be analyzed using multivariate logistic regression with backward stepwise variable selection.

In the final regression model, the modeling performance was evaluated on the validation set. Our model generated a probability of inpatient mortality from 0 to 1 for each admission episodes. The predictive power of the model was calculated using the area under the curve (AUC) in the receiver operating characteristic (ROC) analysis. In order to compare our model with current clinical scores, we also applied Cardiac Arrest Risk Triage (CART) [21] score into the same validation set and compared the performance between CART score and our novel model.

Results

Basic characteristics

A total of 433,187 unique emergency admission episodes were included in this study. Of the 433,187 eligible episodes, 15,758 episodes (3.64%) met the outcome, i.e. inpatient mortality. The mean age of the whole cohort was 62.1 (SD=17.7) years, 50.1% were female (n=216,914), most patients were Singaporean (90.5%, n=392,219), the ethnic compositions were similar to population norms (71.2% for Chinese,12.1% for Malay, 10.6% for Indian and 6.1% for others), 2.1% (n=9144) of the patients received blood gas services in the ED, the mean ED boarding time was 4.78 (SD=3.83) hours and the mean ED consultation waiting time was 0.77 (SD=0.79) hours).

The whole cohort was subsequently divided into the derivation and validation set as displayed in Figure 1. Table 1 shows the statistics of highly similar population in both sets. The derivation set was constitutive of patients with a mean age of 62.1 (SD=17.7), with similar male (49.9%) and female (50.1%) proportion, with the ethnic

breakdown representing the general Singaporean population. Compared to the patients who survived to discharge, patients who died in hospital were older, had shorter ED boarding time and consultation waiting time, and a higher probability of receiving blood gas services while in the ED. They also had lower SPO_2, blood pressure, bicarbonate, and sodium concentration with a higher pulse, respiration rate, FiO_2, and potassium and creatinine concentration.

Univariable Analysis

Table 2 shows the OR and adjusted OR of all demographic, administrative and clinical variables. All variables were respectively significant in the univariate regression in terms of the p-value. We treated vital signs and lab test values as continuous variables and their odds ratios represent the increase or decrease in the odds of inpatient mortality for a one-unit increase in this feature. Observed from the demographical data, patients who were male, Chinese ethnic Singaporean had a higher risk of inpatient mortality. Patients who were foreigners and other races beyond Chinese were unlikely to die in the hospital after emergency admission. Administratively, patients who had shorter consultation waiting time and ED boarding time were more likely to die in hospital. Clinically, patients with a higher pulse, respiration rate, FIO_2, creatinine and potassium concentration and lower blood pressure, SPO_2, bicarbonate, and sodium concentration had a higher risk of inpatient death. All 19 variables were selected for multivariate stepwise analysis as a result of their p-values all below 0.01.

Multivariable Analysis

All variables were used to create the stepwise regression model and no variable was removed through stepwise variable selection. The final model contains 19 variables and the multivariate analysis with the corresponding adjusted odds ratio are shown in Table 2. Older Singaporean with Chinese ethnic had a higher change of inpatient mortality. Although diastolic blood pressure, shift time and day of week were not very significant in multivariate analysis, they were included into the final model after backward stepwise variable selection and due to the clinical judgments [27].

Predictive Model Performance

Our model shows good discriminatory capability on predicting inpatient mortality. On the validation set, the model achieved the AUC of 0.817 (95% CI: 0.810-0.824) with a sensitivity of 73.1% (95% CI: 70.7%-77.6%) and a specificity of 75.4% (95% CI: 70.9%-76.9%) under the optimal threshold (Probability = 0.037) as shown in Figure 2. In contrast, the performance of the existing CART score achieved the AUC of 0.705 (95% CI: 0.697-0.714) with the sensitivity of 72.1% (95% CI: 70.7%-73.6%) and specificity of 56.1% (95% CI: 55.8%-56.4%) under the optimal threshold (CART value = 7). The calibration curve of our developed model is shown in Figure 3.

Discussion

In this study, the main finding is that 19 routinely collected variables from the ED EHR system can be utilized to predict inpatient mortality for the patients after their emergency admission. Our predictive model has better discriminative power than the CART score (AUC, 0.817 vs. 0.705) on the same validation set. The results suggest the possibility of building a reliable inpatient mortality model from the basic demographic, administrative and limited clinical information acquired in the ED when

patients are admitted into the hospital through ED. By deriving a model of inpatient mortality using routinely collected ED data, our study identifies factors associated with inpatient mortality and provides a potentially useful tool for risk stratification of ED patients.

A major strength of our model is the size of the dataset, which was used for deriving this model. This is among the largest datasets used to generate an inpatient mortality predictive model with a cohort of over 430,000 patients in a 10-year period, targeting almost the whole hospital. In addition, it included a large amount of diversity due to Singapore's diverse population. Another advantage of our model is its comprehensiveness, making it applicable to the general patient population presenting to the ED rather than some specific patient subgroups. Furthermore, the application of EHR systems will make our model easy to implement.

There are several reasons why the CART score underperformed our novel model in our study. At first, the CART score did not comprise laboratory test variables. The importance of including routine laboratory test values in the risk predictive model has been demonstrated in other studies. For example, in a study [28] by Churpek and colleagues, including laboratory values in his model contributes important knowledge to the field. Pine et al. [29] and Froom et al. [30] also gave evidence of laboratory values improving predictions of hospital mortality. Secondly, CART was unable to make use of valuable routine administrative data. Guttmann et al. [31] and Parker et al. [32] have previously shown that waiting time, work shifts and other administrative variables were greatly associated with inpatient mortality and hospital admission. In comparison, our model takes both ED administrative data and laboratory test value into account, proving a higher accuracy than the CART score.

Previous researchers have created several predictive tools for inpatient mortality. For example, Prytherch et al. [16] developed the ViEWS score, mainly utilizing vital signs variables to predict mortality for hospitalized patients within 24 hours. The significant predictors of mortality were the pulse, breathing rate, temperature, systolic BP, SPO_2, FiO_2 and mental status. Although vital signs are potential predictors of adverse events, it gives rapid response team (RRT) too short time to respond, especially in a hospital with full capacity or lack of manpower. Since changes in vital signs occur hours before the event, these changes may not be seen at the time of consultation at the ED when potentially high-risk patients have non-discriminatory vital signs similar to that of other healthy patients. Secondly, elderly patients may not have the expected vital signs changes associated with the clinical deterioration and modeling using vital signs alone might miss out cases. It was demonstrated in a study [33] of Churpek and colleagues, who suggests additional predictors of adverse events for elderly patients. Our model is notably different from this because it involved laboratory test values and administrative data besides vital signs and were presumably appropriate for the rapidly aging population in Singapore [34].

Another study [35] in Australia employed multivariable logistic regression of variables from datasets obtained at triage in one hospital to derive and validate a mortality prediction model, Triage Information Mortality Model (TIMM). This TIMM included age, gender, time of year, ambulance, Australasian triage scale and nine chief complaint codes. However, it did not include any physiological variables that were considered as strong predictors and could be obtained conveniently from the EHR

system. In comparison, our model combined demographic, administrative, and physiological variables, which will provide a much more comprehensive profile and capture the sufficient information of the patients in the ED, hence improving the model's predictive power.

Our data analysis also produces some notable findings regarding risk factors related to inpatient mortality. It identified increased age, low blood pressure, high heart rate and elevated creatinine and potassium concentration and decreased sodium and bicarbonate concentration when patients are present to ED as important predictors for inpatient mortality. Besides these factors, our study identified some non-patient factors such as emergency boarding time, day of week and shift time, which can affect patient outcomes. Presenting to ED on Friday or weekend and shift time 24:00 to 8:00 were found to increases risk, consistent with a large study of Aylin and colleagues[36] in the US, which shows 10% higher odds of death for all emergency admission at the weekend compared with admission during a weekday. An excess in mortality may reflect differences in quality of care, potentially as a result of the ED overcrowding, insufficient services, change of shift and slower access to critical investigations. However, the differences in mortality decreased after adjustment for other factors in our analysis Shorter ED boarding time and consultation waiting time become predictors potentially due to severely critical patients with a fast track to admission and intensive resources.

The information needed for this novel model is readily available at the time of consultation at the ED when the first set of laboratory tests are done. When a physician has to make a decision on further management and disposition of the patient. Our model can be deployed for early identification of high-risk patients. Afterward, we can allocate more intensive resources to high-risk patients with a sufficient level of monitoring, increasing nursing attention [37], activation of a rapid response team [38] or medical emergency team (MET) [39]. Thus, through our model, these patients could be seen early after emergency admission and above interventions can be started to avoid severe sudden adverse events during their inpatient stay. Similarly, low-risk patients below the predictive threshold could potentially be safely identified who might not need admission or intensive monitoring and thus save precious in-patient resources. Overall, the good performance, usability and widespread adoption of advanced EHR system make our model easy to integrate into the hospital electronic system such that the probability of inpatient mortality or real-time risk score can be calculated for every patient when they are presented to the ED and ready for admission to hospital. The model can supplement the physician's judgment in decision-making.

Limitation

There are several limitations in this study. First, all variables included in this study are based on EHR and it only contains routinely collected information and does not include all information available that should, in theory, be elicited early when patients present to the ED. For example, comorbidity information or Charlson Comorbidity Index (CCI)[40] was considered as significant predictors. However, they were not available in our current analysis. Other health utilization such as intubation and resuscitation have been proved predictive of overall mortality and should have been included in our model. Furthermore, due to the lack of neurological features such as Glasgow Coma Scale (GCS) score, which were not common variables collected in a

Singaporean hospital. Thus, we were not able to calculate the MEWS score and compare it with our model. In future studies, the GCS and other important features should be recorded and incorporated into prospective investigations. Second, this is a single-site study at a tertiary hospital and our findings may not be generalized to other settings; thus, our results need to be validated in different hospital settings in Singapore or other countries in the future research, especially population consisting of different ethnicities to avoid center-specific bias. Prospective data collection is supposed to explore the clinical value and effect of our model in practice and further prove its efficacy. Third, our model is complex and the calculation should be done electronically. The ability to implement an EHR system varies in a different hospital and lack of features monitored by the system may limit the generalizability of our model.

Conclusion

In summary, we identified several risk factors and developed a novel model for inpatient mortality using 10-year EHR data routinely collected at the ED. The discriminative capability of our model was better than that of the traditional clinical score, CART score. Implementation of our model in the ED can allow accurate and timely identification of a high-risk cohort for interventions during their inpatient stay, resulting in a potential reduction in avoidable inpatient mortality.

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Table 1: Description of the study cohort

	Derivation Set				Validation Set			
	All Admission Episodes (n=333,187)	Discharged (n=321,061)	Inpatient Mortality (n=12,126)	p-Value	All Admission Episodes (n=100,000)	Discharged (n=96,368)	Inpatient Mortality (n=3,632)	p-Value
Demographics								
Age (SD)	62.12 (17.67)	61.79 (17.71)	70.78 (13.92)	<0.001	62.12 (17.65)	61.79 (17.69)	70.86 (13.84)	<0.001
Gender (%)				<0.001				<0.001
Male	166354 (49.9)	159742 (49.8)	6612 (54.5)		49892 (49.9)	47902 (49.7)	1990 (54.8)	
Female	166833(50.1)	161319(50.2)	5514(45.5)		50108(50.1)	48466(50.3)	1642(45.2)	
Nationality (%)				<0.001				<0.001
Singaporean	301661(90.5)	290204(90.4)	11457(94.5)		90558(90.6)	87102(90.4)	3456(95.2)	
Foreigner	31526 (9.5)	30857 (9.6)	669 (5.5)		9442 (9.4)	9266 (9.6)	176 (4.8)	
Race (%)				<0.001				<0.001
Chinese	237147 (71.2)	227418 (70.8)	9729 (80.2)		71196 (71.2)	68242 (70.8)	2954 (81.3)	
Malay	40377 (12.1)	39210 (12.2)	1167 (9.6)		12171 (12.2)	11815 (12.3)	356 (9.8)	
Indian	35259 (10.6)	34466 (10.7)	793 (6.5)		10585 (10.6)	10348 (10.7)	237 (6.5)	
Others	20404 (6.1)	19967 (6.2)	437 (3.6)		6048 (6.0)	5963 (6.2)	85 (2.3)	
ED Administrative Data								
Consultation waiting time (SD)	0.77 (0.80)	0.78 (0.80)	0.48 (0.58)	<0.001	0.77 (0.79)	0.78 (0.79)	0.48 (0.57)	<0.001
ED boarding time (SD)	4.78 (3.83)	4.80 (3.83)	4.35 (3.70)	<0.001	4.78 (3.84)	4.80 (3.84)	4.40 (3.94)	<0.001
Day of week (%)				<0.001				0.002
Midweek	144866 (43.5)	139817 (43.5)	5049 (41.6)		43395 (43.4)	41897 (43.5)	1498 (41.2)	
Monday	55643 (16.7)	53726 (16.7)	1917 (15.8)		16659 (16.7)	16088 (16.7)	571 (15.7)	
Friday	46724 (14.0)	44932 (14.0)	1792 (14.8)		13915 (13.9)	13380 (13.9)	535 (14.7)	
Weekend	85954 (25.8)	82586 (25.7)	3368 (27.8)		26031 (26.0)	25003 (25.9)	1028 (28.3)	
Shift time (%)				0.002				0.243
08:00 to 16:00	167802 (50.4)	161871 (50.4)	5931 (48.9)		50514 (50.5)	48729 (50.6)	1785 (49.1)	

16:00 to 24:00	125745 (37.7)	121075 (37.7)	4670 (38.5)		37896 (37.9)	36480 (37.9)	1416 (39.0)	
24:00 to 8:00	39640 (11.9)	38115 (11.9)	1525 (12.6)		11590 (11.6)	11159 (11.6)	431 (11.9)	
Clinical Data								
Blood gas (%)	6971 (2.1)	6047 (1.9)	924 (7.6)	<0.001	2173 (2.2)	1889 (2.0)	284 (7.8)	<0.001
Pulse (SD)	82.70 (17.02)	82.28 (16.69)	93.85 (21.32)	<0.001	82.71 (16.98)	82.32 (16.66)	93.21 (21.44)	<0.001
Respiration rate (SD)	17.85 (1.74)	17.81 (1.63)	18.81 (3.40)	<0.001	17.84 (1.73)	17.81 (1.63)	18.78 (3.36)	<0.001
FiO_2 (SD)	23.10 (10.14)	22.63 (8.50)	35.43 (27.44)	<0.001	23.07 (10.02)	22.64 (8.46)	34.67 (26.89)	<0.001
SPO_2 (SD)	97.99 (3.18)	98.02 (3.05)	97.14 (5.60)	<0.001	97.98 (3.23)	98.01 (3.07)	97.14 (5.97)	<0.001
Diastolic BP (SD)	71.34 (13.46)	71.49 (13.33)	67.22 (15.81)	<0.001	71.39 (13.55)	71.57 (13.42)	66.65 (15.88)	<0.001
Systolic BP (SD)	133.76 (25.33)	134.12 (25.17)	124.29 (27.58)	<0.001	133.87 (25.44)	134.27 (25.25)	123.16 (27.87)	<0.001
Bicarbonate (SD)	22.80 (3.54)	22.86 (3.43)	21.18 (5.48)	<0.001	22.79 (3.55)	22.85 (3.44)	21.23 (5.44)	<0.001
Creatinine (SD)	146.60 (197.88)	144.91 (197.04)	191.47 (214.24)	<0.001	145.86 (196.34)	144.36 (195.53)	185.80 (212.89)	<0.001
Potassium (SD)	4.16 (0.67)	4.15 (0.66)	4.38 (0.92)	<0.001	4.16 (0.68)	4.15 (0.66)	4.35 (0.89)	<0.001
Sodium (SD)	135.11 (4.85)	135.18 (4.73)	133.29 (7.26)	<0.001	135.12 (4.86)	135.19 (4.72)	133.20 (7.43)	<0.001

ED=Emergency Department, SD= Standard Deviation, ED=Emergency Department, SD= Standard Deviation, BP=Blood Pressure, FiO_2= Fraction of inspired oxygen, SpO_2= Blood Oxygen Saturation

Table 2: Univariable and multivariable analysis

	Unadjusted OR (95% CI)	p-Value	Adjusted OR (95% CI)	Adjusted p-Value
Demographics				
Age	1.034(1.033-1.035)	<0.001	1.035(1.033-1.036)	<0.001
Gender				
Female	Baseline		Baseline	
Male	1.211(1.168-1.256)	<0.001	1.144(1.1-1.19)	<0.001
Nationality				
Singaporean	Baseline		Baseline	
Foreigner	0.549(0.508-0.594)	<0.001	0.898(0.82-0.984)	0.021
Race				
Chinese	Baseline		Baseline	
Malay	0.696(0.654-0.74)	<0.001	0.865(0.809-0.925)	<0.001
Indian	0.538(0.5-0.579)	<0.001	0.69(0.638-0.746)	<0.001
Others	0.512(0.464-0.564)	<0.001	0.773(0.692-0.862)	<0.001
ED Administrative				
Consultation waiting time	0.437(0.42-0.454)	<0.001	0.683(0.659-0.709)	<0.001
ED boarding time	0.96(0.954-0.966)	<0.001	0.981(0.975-0.987)	<0.001
Day of Week				
Midweek	Baseline		Baseline	
Monday	0.988(0.937-1.042)	0.661	1.009(0.953-1.068)	0.761
Friday	1.104(1.045-1.167)	<0.001	1.084(1.022-1.149)	0.007
Weekend	1.129(1.08-1.181)	<0.001	1.001(0.954-1.051)	0.954
Shift time				
8:00 to 16:00	Baseline		Baseline	
16:00 to 24:00	1.053(1.012-1.095)	0.01	1.023(0.981-1.067)	0.288
24:00 to 8:00	1.092(1.031-1.156)	0.003	0.94(0.883-1)	0.05
Clinical Data				
Blood gas (Yes=1, No=0)	4.297(4-4.617)	<0.001	1.224(1.121-1.336)	<0.001
Pulse	1.035(1.034-1.036)	<0.001	1.025(1.024-1.026)	<0.001
Respiration rate	1.2(1.192-1.208)	<0.001	1.034(1.027-1.042)	<0.001
FiO_2	1.04(1.039-1.04)	<0.001	1.028(1.027-1.029)	<0.001
SPO_2	0.966(0.963-0.969)	<0.001	0.979(0.976-0.983)	<0.001
Diastolic BP	0.975(0.973-0.976)	<0.001	0.999(0.997-1.001)	0.18
Systolic BP	0.984(0.983-0.984)	<0.001	0.985(0.984-0.986)	<0.001
Bicarbonate	0.889(0.885-0.893)	<0.001	0.967(0.962-0.972)	<0.001
Creatinine	1.001(1.001-1.001)	<0.001	1.001(1.001-1.001)	<0.001
Potassium	1.528(1.494-1.562)	<0.001	1.159(1.129-1.189)	<0.001
Sodium	0.938(0.935-0.941)	<0.001	0.961(0.958-0.964)	<0.001

ED=Emergency Department, SD= Standard Deviation, BP=Blood Pressure, OR=Odd Ratio, FiO_2= Fraction of inspired oxygen, SpO_2= Blood Oxygen Saturation

Author Contributions

FX, NL, and MEHO conceived and designed the study. NL, MEHO, and BC supervised the study. FX and SXW performed data retrieval and preprocessing. FX analyzed the data. FX, NL, YA, LLL, AFWH, SSWL, DBM, MEHO and BC interpreted the results. FX wrote the first draft of the paper and all authors critically revised the paper and gave final approval for publication.

Competing interests: None declared

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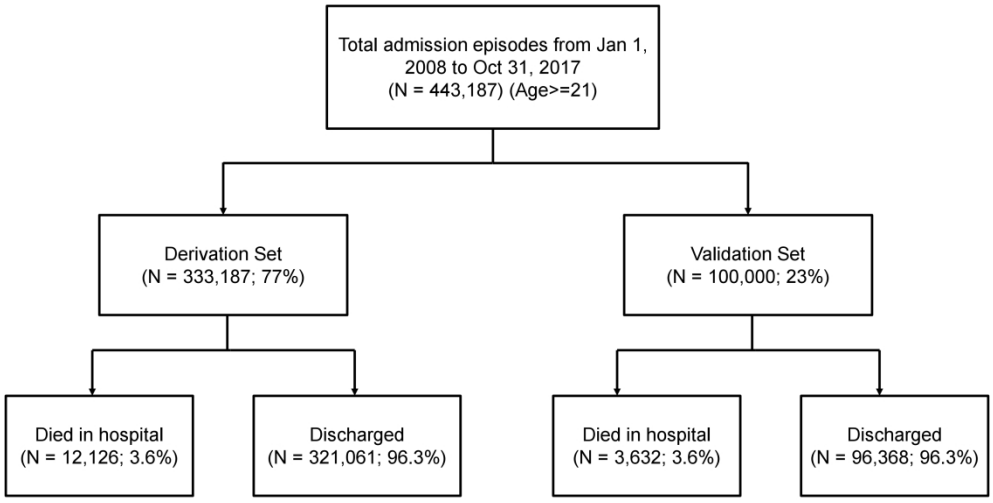
Ethics approval:
This study was approved by Singapore Health Services (SingHealth) Centralized Institutional Review Board (CIRB Ref 2017/2666) with a waiver of informed consent.

Provenance and peer review: Not commissioned; externally peer reviewed.

Data sharing statement: Details of the variables and derived predictive model are available from the corresponding author.

Word count: 3360



Flow of patients' emergency admissions.

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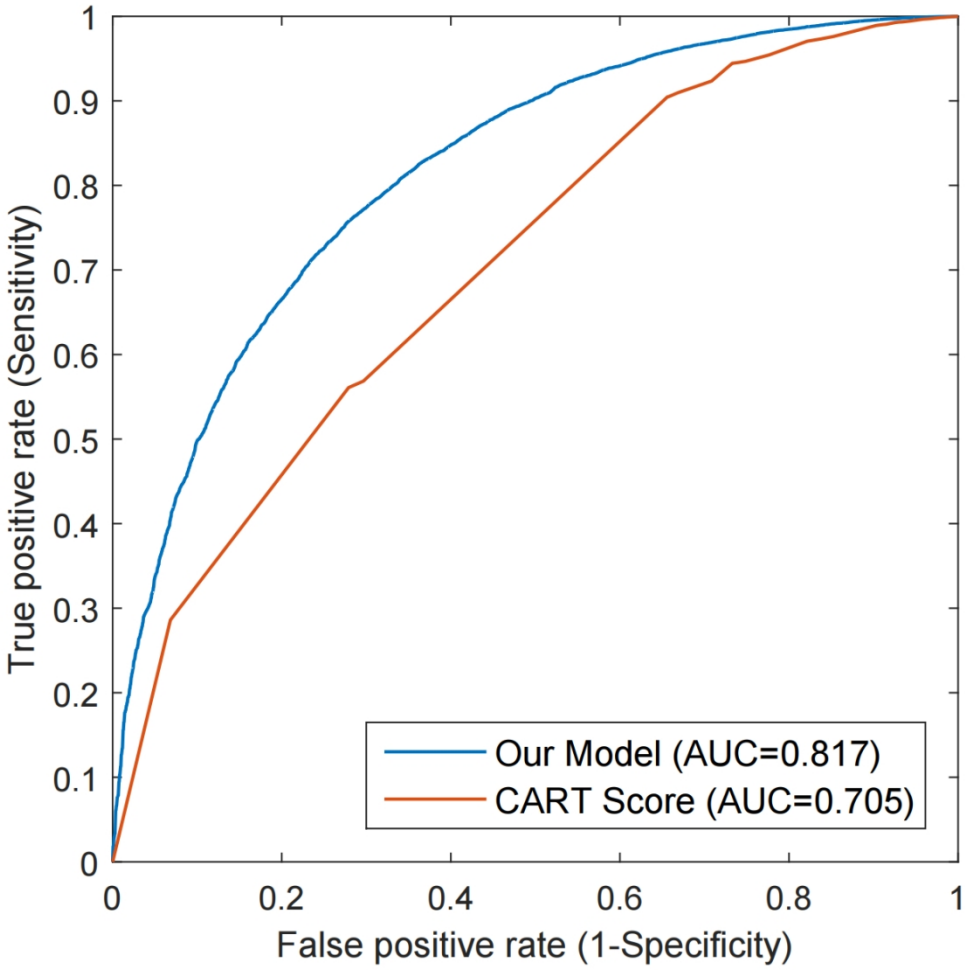

Receiver operating characteristic (ROC) curves of our model and CART score on the validation set.

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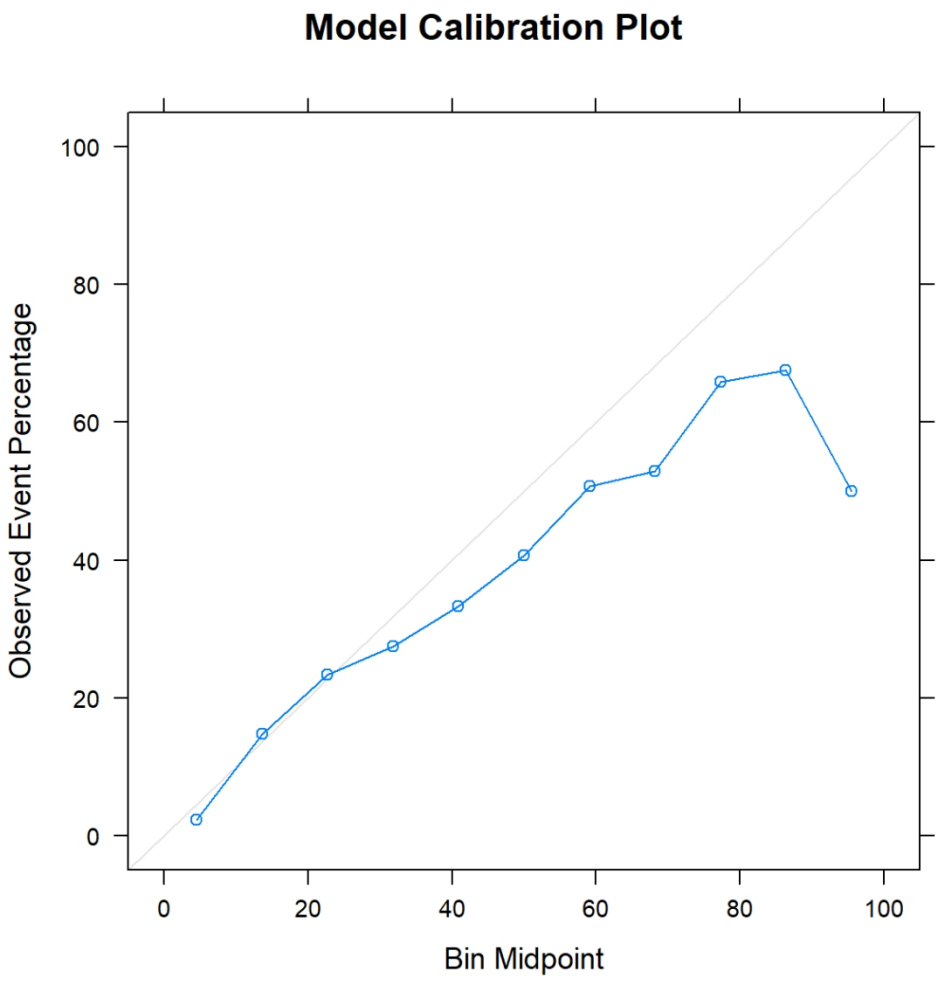

Model calibration curve on the validation set.

141x141mm (216 x 216 DPI)

TRIPOD Checklist: Prediction Model Development and Validation

Section/Topic	Item		Checklist Item	Page
Title and abstract				
Title	1	D;V	Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted.	1
Abstract	2	D;V	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.	1-2
Introduction				
Background and objectives	3a	D;V	Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models.	3
	3b	D;V	Specify the objectives, including whether the study describes the development or validation of the model or both.	3
Methods				
Source of data	4a	D;V	Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable.	4
	4b	D;V	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.	
Participants	5a	D;V	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres.	4
	5b	D;V	Describe eligibility criteria for participants.	4
	5c	D;V	Give details of treatments received, if relevant.	
Outcome	6a	D;V	Clearly define the outcome that is predicted by the prediction model, including how and when assessed.	4
	6b	D;V	Report any actions to blind assessment of the outcome to be predicted.	
Predictors	7a	D;V	Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured.	4
	7b	D;V	Report any actions to blind assessment of predictors for the outcome and other predictors.	
Sample size	8	D;V	Explain how the study size was arrived at.	5
Missing data	9	D;V	Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.	5
Statistical analysis methods	10a	D	Describe how predictors were handled in the analyses.	4-5
	10b	D	Specify type of model, all model-building procedures (including any predictor selection), and method for internal validation.	4-5
	10c	V	For validation, describe how the predictions were calculated.	5
	10d	D;V	Specify all measures used to assess model performance and, if relevant, to compare multiple models.	5
	10e	V	Describe any model updating (e.g., recalibration) arising from the validation, if done.	6
Risk groups	11	D;V	Provide details on how risk groups were created, if done.	
Development vs. validation	12	V	For validation, identify any differences from the development data in setting, eligibility criteria, outcome, and predictors.	5
Results				
Participants	13a	D;V	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.	5
	13b	D;V	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.	5
	13c	V	For validation, show a comparison with the development data of the distribution of important variables (demographics, predictors and outcome).	5
Model development	14a	D	Specify the number of participants and outcome events in each analysis.	5
	14b	D	If done, report the unadjusted association between each candidate predictor and outcome.	6
Model specification	15a	D	Present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point).	6
	15b	D	Explain how to the use the prediction model.	8
Model performance	16	D;V	Report performance measures (with CIs) for the prediction model.	6
Model-updating	17	V	If done, report the results from any model updating (i.e., model specification, model performance).	
Discussion				
Limitations	18	D;V	Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).	8-9
Interpretation	19a	V	For validation, discuss the results with reference to performance in the development data, and any other validation data.	7-8
	19b	D;V	Give an overall interpretation of the results, considering objectives, limitations, results from similar studies, and other relevant evidence.	6-8
Implications	20	D;V	Discuss the potential clinical use of the model and implications for future research.	8
Other information				
Supplementary information	21	D;V	Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets.	
Funding	22	D;V	Give the source of funding and the role of the funders for the present study.	16

*Items relevant only to the development of a prediction model are denoted by D, items relating solely to a validation of a prediction model are denoted by V, and items relating to both are denoted D;V. We recommend using the TRIPOD Checklist in conjunction with the TRIPOD Explanation and Elaboration document.