

Development and Evaluation of Models to Predict Readmission or Death After Discharge from Intensive Care

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Abstract

Background

Patients being discharged from the intensive care unit (ICU) have variable risks of subsequent readmission or death; however, there is limited understanding of how to predict individual patient risk. We sought to derive risk prediction models for ICU readmission or death after ICU discharge to guide clinician decision-making.

Methods

Systematic review and meta-analysis to identify risk factors. Development and validation of risk prediction models using two retrospective cohorts of patients discharged alive from medical-surgical ICUs (n = 3 ICUs, n = 11,291 patients; n = 14 ICUs, n = 11,400 patients). Models were developed using literature and data-derived weighted coefficients.

Results

Sixteen variables identified from the systematic review were used to develop four risk prediction models. In the validation cohort there were 795 (7%) patients who were re-admitted to ICU and 703 (7%) patients who died after ICU discharge. The area under the curve (AUROC) for ICU readmission for the literature (0.615 [95%CI: 0.593, 0.637]) and data (0.652 [95%CI: 0.631, 0.674]) weighted models showed poor discrimination. The AUROC for death after ICU discharge for the literature (0.708 [95%CI: 0.687, 0.728]) and local data weighted (0.752 [95%CI: 0.733, 0.770]) models showed good discrimination. The negative predictive values for ICU readmission and death after ICU discharge ranged from 94%-98%.

Conclusions

Identifying risk factors and weighting coefficients using systematic review and meta-analysis to develop prediction models is feasible and can identify patients at low risk of ICU readmission or death after ICU discharge.

Introduction

Transitions of care are high-risk periods in healthcare delivery.[1, 2] This is particularly true for patients recovering from critical illness as they transfer from the intensive care unit (ICU) to a less-acute hospital ward.[3–5] Although these patients have begun to regain their health and no longer require life-sustaining technologies,[4] there are risks associated with discharge to a more resource limited environment (which usually includes a change in patient-provider ratio),[6, 7] including adverse events, ICU readmission and death after ICU discharge.[8–11]

The ICU discharge process begins with the decision to transfer the patient, which requires clinical judgment.[12, 13] Clinical decision-support tools can aid clinicians to make better decisions. A limited literature suggests that clinical decision-support tools may help clinicians with ICU discharge decision-making,[14–17] however, most existing tools are limited to a few select risk factors or to one outcome (e.g., ICU readmission).[18, 19] Moreover, the existing published tools have undergone limited validations, employ highly variable risk factors and exhibit mixed degrees of potential clinical utility.[20] We conducted a multi-methods study to develop and evaluate models to predict patient readmission to ICU or death after ICU discharge. Our objective was to derive risk prediction models using a combination of risk factors that have been shown to be consistently associated with readmission to ICU or death after ICU discharge in the literature. The validity of the models was then evaluated in a large independent cohort of critically ill patients.

Methods

We employed multiple methods over three distinct phases of work to derive and validate individual prediction models for ICU readmission and death after ICU discharge. First, we conducted a *systematic review* and meta-analysis to identify risk factors previously reported to be consistently associated with ICU readmission or death after discharge from a medical-surgical ICU. Second, we used the risk factors identified to inform the *derivation* of risk prediction models in a retrospective cohort of patients. Finally, we

evaluated the operating characteristics (*validation*) of the derived models in an independent cohort of patients. ICU readmission was defined as a patient with an unplanned readmission to ICU during the index hospitalization. Death after ICU discharge was defined as patients discharged alive from ICU who later died during the index hospitalization. Model development and validation are reported according to the TRIPOD statement.[21]

Identification of Risk Factors

We conducted a systematic review and meta-analysis in accordance with the Preferred Reporting for Systematic Reviews and Meta-Analyses (PRISMA).[22] The search was conducted on April 1, 2016 and included three term clusters: intensive care units, patient discharge, and ICU readmission/ death after ICU discharge. Two reviewers (JMB, MLP, KJM, RBM) independently reviewed titles and abstracts, and subsequently full text citations, including articles meeting the following criteria: 1) cohort study or controlled trial; 2) original data on human adult ICU patients (≥ 18 years); 3) explored one or more risk factors present at ICU discharge; 4) examined ICU readmission and/or in-hospital mortality as an outcome; 5) outcome evaluated after ICU discharge but prior to hospital discharge; and 6) reported summary measure of association (adjusted odds ratio [OR]) or adequate raw data for its calculation. Significant clinical and methodological heterogeneity between studies was anticipated and therefore a meta-analysis of identified risk factors was performed using the DerSimonian and Laird method for random-effects models.[23] The detailed methods of the *systematic review* are presented in Appendix 1. Risk factors were defined as consistently associated with an outcome if: there were two or more studies examining the risk factors and the 95% confidence interval (CI) of the pooled OR did not include the null value. These risk factors were mapped to available data points from the data repository. Operational definitions of candidate risk factors were derived from the authors' definitions of the included studies (see Appendix 2).

Patients

We identified two distinct cohorts of consecutive adult medical-surgical patients (≥ 18 years) discharged alive from ICUs in Alberta, Canada that used electronic medical record systems during the study period for the *derivation* (three ICUs incorporating patients admitted between January 1, 2002 and December 31, 2011) and *validation* (14 ICUs incorporating patients admitted between January 1, 2014 and September 30, 2016) of the risk models. Patients were excluded if the: 1) patient was not discharged from a medical-surgical ICU (e.g., burn ICU); 2) discharge was not to a hospital ward (e.g., discharged directly home); or 3) patient was < 18 years of age. For patients with multiple ICU readmissions within the index hospital admission, or multiple hospital admissions during the study period, only data from the first ICU admission for the first hospitalization was used in the analysis. Patients were identified and data collected from linked clinical and administrative databases previously used for quality improvement and research initiatives (eCritical,[24] Discharge Abstract Database [DAD],[25] Sunrise Clinical Manager [SCM][26]).

Weighting of Risk Scoring Systems

Two different approaches to model development were used. The *Literature weighted* method applied a literature-based approach using the beta-coefficients identified through the meta-analysis to weight the selected covariates, The *Local data weighted* method applied weights derived from including all the covariates selected from the meta-analysis in a logistic regression model in the *derivation* cohort of patients to determine their coefficients. For both outcomes of interest (ICU Readmission & death after ICU discharge), the models included all factors consistently associated with risk of the respective outcomes that could be mapped to the administrative datasets. The baseline risk (β_0) of the patients included in the *derivation* cohort was applied to the models for both the *Literature weighted* and *Local data weighted* methods. A total of four models were developed using two methods of model construction for testing in the external *validation* cohort (both *literature weighted* & *local data weighted* ICU readmission models & death after ICU discharge models).

Statistical Analysis

Patient and hospital characteristics were explored using descriptive statistics. Using a two-tailed alpha of 5%, we determined the discrimination characteristics for the *Literature weighted* (model *validation*) and *Local data weighted* (model *derivation* and *validation*) prediction models using area under the receiver operator characteristic (AUROC) curves.[27, 28] Clinically relevant risk thresholds of ICU readmission and death after ICU discharge (3%, 5%, 10%) were applied to the models to examine performance based on positive and negative predictive values.[18, 29] We assessed model calibration using observed versus expected plots across deciles of predicted risk, and the Hosmer-Lemeshow χ^2 goodness of fit test.[27, 28, 30] Calibration slopes were also evaluated

for each model during model *validation* by plotting the observed versus predicted values ($b > 1$ represents over-fitting of the model). [31, 32]

Results

Systematic Review

The literature search identified 26,897 unique citations from which 832 abstracts were judged to be eligible for full-text review. We identified 65 full-text articles for inclusion in the review (see Appendix 3). The main reasons for citation exclusion during the full text review were studies that: did not include outcome of interest ($n = 310$), were not original research ($n = 143$) or were not related to the ICU discharge process ($n = 120$). Inter-rater agreement for full-text inclusion was good ($K = 0.85$, 95% CI: 0.56, 0.94). Appendix 4 presents the study characteristics of the included studies. The forest plots of the random-effects models for ICU readmission and death after ICU discharge are depicted in Appendices 5 and 6.

Risk factors independently associated with ICU readmission included age (years), history of cancer, history of immunosuppression, history of renal disease, history of respiratory disease, Charlson Comorbidity Score ≥ 1 , ICU admission from ward, Eosinopenia, Acute Physiology and Chronic Health Evaluation (APACHE II) score > 9 on admission and ICU length of stay (days) (see Appendix 7). Risk factors independently associated with death after ICU discharge included age (years), male, history of liver disease, duration of hospital stay prior to ICU admission (days), ICU admission from ward, medical admission, APACHE II score > 9 on admission, ICU readmission and night-time discharge (see Appendix 8). Goals of care at ICU discharge was found to be strongly associated with death after ICU discharge; however, owing to the limited availability of data for this variable within the *validation* cohort this covariate was not included in the final models.

Patient Characteristics and Outcomes

Appendices 9 and 10 depict the flow of patients in the *derivation* and *validation* cohorts, respectively. Of the 18,756 patient records in the *derivation* cohort, 11,291 were eligible for inclusion in the study. Of the 17,841 patient records in the *validation* cohort, 11,400 were eligible for inclusion in the study. Table 1 describes the patient characteristics of the *derivation* and *validation* cohorts. The typical patient in the *derivation* cohort had a medical reason for admission (48%), was male (59%) with a median age of 58 years (interquartile range [IQR] 43, 71) and an APACHE II score on admission of 16 (IQR 12, 19). The typical patient in the *validation* cohort had broadly similar characteristics. Overall, 9% and 7% of patients discharged alive from ICU were readmitted within the index hospitalization (*derivation* and *validation*, respectively), and 7% of patients discharged alive from ICU (excluding those with ICU readmission) died after ICU but prior to hospital discharge in both the *derivation* and *validation* cohorts.

Table 1
Patient Characteristics of Derivation and Validation Cohorts

CHARACTERISTIC	Derivation (n = 11 291)	Validation (n = 11 400)
Male	6627 (59)	6693 (59)
Age, y median (IQR)	58 (43, 71)	60 (46, 71)
<i>Comorbidities</i>		
History of Cancer	1542 (14)	1300 (13)
History of Immunosuppression	40 (0.4)	41 (0.4)
History of Liver Disease	308 (3)	362 (4)
History of Renal Disease	1207 (11)	1674 (15)
History of Respiratory Disease	2021 (18)	1697 (17)
History of Diabetes	2116 (19)	2580 (26)
History of Chronic Heart Disease	2634 (23)	1473 (15)
≥ 1 Charlson Comorbidity	7299 (65)	7773 (68)
Charlson Index, median (IQR)	1 (0, 3)	1 (0, 3)
<i>Admission Class</i>		
Medical	5416 (48)	6024 (54)
Neurocritical	961 (9)	637 (6)
Surgical	4012 (36)	3561 (32)
Trauma	856 (8)	979 (9)
<i>Location Before ICU Admission</i>		
Emergency Department	4086 (36)	4648 (41)
Hospital Ward	2132 (19)	2578 (23)
Operating Room	2998 (27)	2676 (23)
Other	2065 (18)	1492 (13)
APACHE II Score on Admission, median (IQR)	16 (12, 19)	18 (13, 24)
APACHE II > 9 on admission	9799 (87)	10260 (90)
Pre-ICU hospital length of stay, days, median (IQR)	0 (0, 1)	0 (0, 1)
ICU readmission during index hospitalization	926 (8)	833 (7)
<i>Interventions Received in ICU</i>		
Mechanical Ventilation	8751 (78)	7263 (64)
Mechanical Ventilation Duration, days median (IQR)*	3 (2, 7)	2 (1, 5)
Continuous Renal Replacement Therapy	321 (3)	477 (4)
Continuous Renal Replacement Therapy Duration, days median (IQR)*	5 (3, 9)	4 (2, 6)
<i>Patient Characteristics on ICU Discharge</i>		
*Median duration among those patients receiving mechanical ventilation or continuous renal replacement therapy		
** Includes deaths in ICU		

CHARACTERISTIC	Derivation (n = 11 291)	Validation (n = 11 400)
Eosinopenia at Discharge	3596 (32)	3361 (29)
ICU Length of Stay, days median (IQR)	3 (2, 7)	4 (2, 7)
Night-time discharge (17:00–07:59)	4869 (43)	4857 (43)
<i>Patient Characteristics on Hospital Discharge</i>		
Hospital Length of Stay, days median (IQR)	17 (10, 37)	15 (8, 31)
Hospital Mortality**	1050 (9)	940 (8)
<i>Study Outcomes</i>		
ICU Readmission	895 (9)	795 (7)
Death after ICU discharge	776 (7)	703 (7)
*Median duration among those patients receiving mechanical ventilation or continuous renal replacement therapy		
** Includes deaths in ICU		

Table 2 outlines the risk factors included in the ICU readmission and death after ICU discharge models, and the distribution of the patients in the *derivation* and *validation* cohorts across the selected risk factors. In the *derivation* cohort, patients who were readmitted to ICU were more often initially admitted from a hospital ward when compared to patients not readmitted to ICU (24% versus 18%, $p < .001$). Readmitted patients were also more likely to have one or more Charlson comorbidities (82% versus 61%, $p < .001$) and an APACHE II score > 9 on admission to ICU (93% versus 85%, $p < .001$) compared to those patients not readmitted to ICU. Patients who died after ICU discharge, but prior to hospital discharge were more often admitted from a hospital ward (30% versus 18%, $p < .001$) and to have an APACHE II score > 9 on admission to ICU (98% versus 85%, $p < .001$) compared to those patients discharged alive from hospital.

Table 2

Distribution of Patients across risk factors for ICU Readmission or Death After ICU Discharge*

Candidate Risk Factor	Model Derivation Cohort (n = 11 291)						Model Validation Cohort (n = 11 400)					
	ICU Readmission			Death after ICU			ICU Readmission			Death after ICU		
	Yes n = 895 (%)	No n = 9,620 (%)	p- value	Yes n = 776 (%)	No n = 9,620 (%)	p- value	Yes n = 795 (%)	No n = 9,902 (%)	p- value	Yes n = 703 (%)	No n = 9,902 (%)	p- value
Male	572 (64)	5631 (59)	.002	424 (55)	5631 (59)	.036	507 (64)	5775 (58)	.003	411 (58)	5775 (58)	.941
Age, y, median (IQR)	63 (50, 73)	56 (41, 70)	< .001	73 (62, 80)	56 (41, 70)	< .001	62 (53, 71)	59 (45, 70)	< .001	71 (60, 80)	59 (45, 70)	< .001
<i>Comorbidities</i>												
History of Cancer	153 (17)	1233 (13)	< .001	156 (20)	1233 (13)	< .001	124 (19)	1056 (12)	< .001	120 (19)	1056 (12)	< .001
History of Immunosuppression	4 (0.5)	33 (0.3)	.388	3 (0.4)	33 (0.3)	.510	0 (0)	36 (0.4)	.173	5 (1)	36 (0.4)	.195
History of Liver Disease	61 (7)	190 (2)	< .001	57 (7)	190 (2)	< .001	54 (8)	241 (3)	< .001	67 (11)	241 (3)	< .001
History of Renal Disease	173 (19)	848 (9)	< .001	186 (24)	848 (9)	< .001	189 (24)	1286 (13)	< .001	199 (28)	1286 (13)	< .001
History of Respiratory Disease	179 (20)	1649 (17)	.031	193 (25)	1649 (17)	< .001	129 (20)	1443 (16)	.012	125 (20)	1443 (16)	.027
History of Diabetes	226 (25)	1684 (18)	< .001	206 (27)	1684 (18)	< .001	187 (29)	2185 (25)	.011	208 (33)	2185 (25)	< .001
History of Chronic Heart Disease	347 (39)	1973 (21)	< .001	314 (40)	1973 (21)	< .001	80 (28)	1260 (15)	< .001	133 (22)	1260 (15)	< .001
≥ 1 Charlson Comorbidity	734 (82)	5855 (61)	< .001	710 (91)	5855 (61)	< .001	662 (83)	6498 (66)	< .001	613 (87)	6498 (66)	< .001
Charlson Index, median (IQR)	2 (1, 4)	1 (0, 2)	< .001	3 (1, 5)	1 (0, 2)	< .001	2 (1, 3)	1 (0, 2)	< .001	2 (1, 4)	1 (0, 2)	< .001
<i>Admission Class</i>												
Medical	417 (47)	4538 (47)	.008	461 (60)	4538 (47)	< .001	408 (52)	5192 (53)	.040	424 (61)	5192 (53)	< .001
Neurocritical	73 (8)	801 (8)		87 (11)	801 (8)		34 (4)	533 (5)		70 (10)	533 (5)	
Surgical	355 (40)	3446 (36)		211 (27)	3446 (36)		289 (37)	3103 (32)		169 (24)	3103 (32)	
Trauma	48 (5)	793 (8)		15 (2)	793 (8)		58 (7)	891 (9)		30 (4)	891 (9)	
<i>Location Before ICU Admission</i>												
Emergency Department	245 (27)	3579 (37)	< .001	262 (34)	3579 (37)	< .001	239 (30)	4153 (42)	< .001	256 (36)	4153 (42)	< .001

*Bolded cells represent risk factors included in prediction models

	Model Derivation Cohort (n = 11 291)						Model Validation Cohort (n = 11 400)					
Hospital Ward	216 (24)	1683 (18)		233 (30)	1683 (18)		248 (31)	2066 (21)		264 (38)	2066 (21)	
Operating Room	242 (27)	2615 (27)		141 (18)	2615 (27)		224 (28)	2336 (24)		116 (17)	2336 (24)	
Other	192 (21)	1733 (18)		140 (18)	1733 (18)		84 (11)	1341 (14)		67 (10)	1341 (14)	
APACHE II Score on Admission, median (IQR)	17 (14, 21)	15 (11, 19)	<.001	21 (17, 25)	15 (11, 19)	<.001	20 (15, 26)	17 (13, 23)	<.001	24 (19, 29)	17 (13, 23)	<.001
APACHE II > 9 on admission	830 (93)	8211 (85)	<.001	758 (98)	8211 (85)	<.001	772 (97)	8791 (89)	<.001	697 (99)	8791 (89)	<.001
Pre-ICU length of stay, d, median (IQR)	0 (0, 3)	0 (0, 1)	<.001	1 (0, 6)	0 (0, 1)	<.001	0 (0, 3)	0 (0, 1)	<.001	1 (0, 5)	0 (0, 1)	<.001
ICU readmission ever	895 (100)	31 (0.3)	<.001	0 (0)	31 (0.3)	.167	795 (0)	35 (0.3)	<.001	3 (0.4)	35 (0.3)	.738
<i>Interventions Received in ICU</i>												
Mechanical Ventilation	746 (83)	7378 (77)	<.001	627 (81)	7378 (77)	.009	555 (70)	6235 (63)	<.001	473 (67)	6235 (63)	.022
Mechanical Ventilation, d median (IQR)	4 (3, 9)	3 (2, 7)	<.001	5 (3, 10)	3 (2, 7)	<.001	2 (1, 5)	2 (1, 5)	<.001	4 (1, 8)	2 (1, 5)	<.001
Continuous Renal Replacement Therapy	63 (7)	203 (2)	<.001	55 (7)	203 (2)	<.001	59 (7)	370 (4)	<.001	48 (7)	370 (4)	<.001
Continuous Renal Replacement Therapy, d median (IQR)	5 (3, 14)	5 (3, 9)	.467	5 (3, 10)	5 (3, 9)	.607	4 (2, 6)	4 (2, 6)	.953	4 (2, 6)	3 (2, 6)	.377
<i>Patient Characteristics on ICU Discharge</i>												
Eosinopenia at Discharge	279 (31)	3047 (32)	.758	270 (35)	3047 (32)	.073	227 (29)	2901 (29)	.657	233 (33)	2901 (29)	.031
ICU Length of Stay, d median (IQR)	4 (2, 10)	3 (1, 7)	<.001	5 (2, 10)	3 (1, 7)	<.001	4 (2, 9)	4 (2, 7)	<.001	5 (3, 10)	4 (2, 7)	<.001
Night-time discharge (17:00–07:59)	428 (48)	4052 (42)	.001	389 (50)	4052 (42)	<.001	365 (46)	4165 (42)	.035	327 (47)	4165 (42)	.021
<i>Patient Characteristics on Hospital Discharge</i>												
Hospital Length of Stay, d median (IQR)	42 (23, 75)	16 (9, 33)	<.001	19 (10, 40)	16 (9, 33)	.002	38 (21, 70)	14 (8, 28)	<.001	20 (11, 38)	14 (8, 28)	<.001
<i>Study Outcomes</i>												
ICU Readmission	895 (100)	0 (0)		–	–		795 (100)	0 (0)		–	–	

*Bolded cells represent risk factors included in prediction models

	Model Derivation Cohort (n = 11 291)				Model Validation Cohort (n = 11 400)			
Post-ICU Mortality	–	–	776 (100)	0 (0)	–	–	703 (100)	0 (0)
*Bolded cells represent risk factors included in prediction models								

In the *validation* cohort, patients who were readmitted to ICU compared to those patients not readmitted, more often had at least one Charlson comorbidity (83% versus 66%, $p < .001$) and an APACHE II score > 9 on admission to ICU (97% versus 89%, $p < .001$). Patients who died after ICU discharge, but prior to hospital discharge were more often admitted from a hospital ward (38% versus 21%, $p < .001$) and had an APACHE II score > 9 on admission to ICU (97% versus 89%, $p < .001$) compared to those patients discharged alive from hospital.

Risk Scoring System Performance

Model Derivation

Appendix 11 describes the operating characteristics of the ICU Readmission and death after ICU discharge models performance in the *derivation* cohort. The ICU Readmission model (*Local data weighted*) showed poor predictive accuracy (AUROC: 0.675 [95%CI: 0.657, 0.693]), whereas the death after ICU discharge model showed good predictive accuracy (AUROC: 0.792 [95%CI: 0.777, 0.807]).

Model performance was compared using a complete case analysis, imputing missing values (assuming absence of eosinopenia) with no significant difference in model performance.

Model Validation

Table 3 describes the operating characteristics of the ICU readmission and death after ICU discharge models in the *validation* cohort. The AUROC for the ICU readmission models for both the *Literature weighted* (AUROC: 0.615 [95%CI: 0.593, 0.637]) and *Local data weighted* (AUROC: 0.652 [95%CI: 0.631, 0.674]) methods showed poor discrimination. The calibration of the *Local data weighted* model (Fig. 1) was better than for the *Literature weighted* model (Fig. 2). The AUROC for the death after ICU discharge models for both *Literature weighted* (AUROC: 0.708 [95%CI: 0.687, 0.728]) and *Local data weighted* (AUROC: 0.752 [95%CI: 0.733, 0.770]) methods showed good discrimination. The calibration of the *Local data weighted* model (Fig. 3) was better than for to the *Literature weighted* model (Fig. 4).

Table 3
ICU Readmission and Death after ICU Discharge Models in the *Validation* Cohort

Literature weighted	ICU Readmission			Death After ICU Discharge		
	ROC: 0.615 (95% CI: 0.593, 0.637)			ROC: 0.708 (95% CI: 0.687, 0.728)		
	10% Predicted Probability*	5% Predicted Probability*	3% Predicted Probability*	10% Predicted Probability*	5% Predicted Probability*	3% Predicted Probability*
Sensitivity	19%	86%	100%	43%	79%	94%
Specificity	89%	28%	0%	84%	48%	22%
Positive Predictive Value	12%	8%	7%	16%	10%	8%
Negative Predictive Value	94%	97%	-	95%	97%	98%
Correctly Classified	85%	32%	7%	82%	50%	27%
Local data weighted	ICU Readmission			Death After ICU Discharge		
	ROC: 0.652 (95% CI: 0.631, 0.674)			ROC: 0.752 (95% CI: 0.733, 0.770)		
	10% Predicted Probability	5% Predicted Probability*	3% Predicted Probability*	10% Predicted Probability*	5% Predicted Probability*	3% Predicted Probability*
Sensitivity	27%	83%	97%	54%	82%	92%
Specificity	86%	38%	10%	81%	52%	34%
Positive Predictive Value	13%	9%	7%	17%	11%	9%
Negative Predictive Value	94%	97%	98%	96%	98%	98%
Correctly Classified	82%	41%	16%	79%	54%	38%
*Model operating characteristics reported using the predicted probabilities of 10%, 5% and 3% of patients discharged alive from ICU experience the outcome of interest prior to hospital discharge.						

Discussion

Four prediction models for ICU readmission (n = 2) and death after ICU discharge (n = 2) were developed using two approaches to model building: *Literature weighted* and *Local data weighted* approaches. The prediction models for ICU readmission showed limited discrimination whereas the death after ICU discharge models showed considerably better discrimination. Both sets of models had high negative predictive values. These findings suggest that the use of systematic review to identify risk factors, and meta-analysis to derive variable weights for development of clinical prediction models in critical care is feasible and produces similar results to data derived models. Further evaluation of the clinical application of the derived model for death after ICU discharge is warranted.

The models developed were primarily able to identify patients at low risk of ICU readmission or death after ICU discharge, suggesting they may help identify patients at low risk for these complications and inform early discharge planning.

What are the implications of these observations for clinicians, managers and researchers?

One, there is clearly a need to develop new approaches to predicting ICU readmission. The poor discrimination ability of the *Literature weighted* and *Local data weighted* models is consistent with a growing body of evidence that suggests that the primary factors influencing ICU readmission are unknown.[33] In fact, Brown et al. have suggested that most readmissions to ICU are about as predictable as a random event and therefore not a good indicator of quality of care.[34] Our data models reinforce those observations and the need for novel approaches to predicting ICU readmission.

Two, death after ICU discharge can be predicted with reasonable accuracy. Our findings are consistent with other models in the literature, such as the ICU Discharge Readiness Score by Badawi and Breslow.[35] The implication is that risk prediction models may be able to improve clinical decision-making. Studies of clinical outcomes after ICU discharge have suggested that physicians have limited ability to predict which patients will experience adverse events, ICU readmission or death after ICU discharge.[36, 37] Evaluation of the clinical application of the derived model for death after ICU discharge is warranted.

Three, although the ICU readmission models in this study do not show promise for predicting which patients will be readmitted, they did have good negative predictive values. This suggests that the models may be effective at identifying patients at low risk for readmission. Interestingly the majority of predictors included in the models were fixed at the time of ICU admission (i.e., not modifiable over the course of stay in ICU), raising the possibility that the models could be applied shortly after patient admission to the ICU to identify those for whom early discharge planning may be appropriate. It is possible that machine learning algorithms may be more effective at identifying modifiable predictors to allow clinicians to modify patient risk through clinical decision-making.[38, 39] The death after ICU discharge models could also be used in a similar manner and given their better predictive abilities could be used to guide physician decision-making in considering delaying ICU discharge, or identifying high priority patients for follow-up by ICU outreach teams.[40, 41]

Four, the use of systematic reviews to identify risk factors for development of clinical prediction models in critical care is feasible. The potential value of such an approach is that it takes advantage of aggregate global research to inform model development. Once candidate risk factors have been identified, there is a small improvement in model discrimination when local data are used to determine weights as opposed to measures of association from a meta-analysis. Grams et al used a similar approach of random-effects modeling of demographics and health factors to predict risk of end-stage renal disease in kidney donor candidates.[42] The practical implication is that healthcare decision-makers can develop and validate prediction models for similar populations elsewhere without necessarily having to locally rederive models, potentially increasing the pace of predictive model development and application.

The findings of this study should be considered in the context of its strengths and limitations. There are three limitations of note. First, the studies identified as part of our systematic review used heterogeneous definitions for the time to the event for outcomes of interest. To minimize bias in the resulting pooled measures of association we needed to exclude some studies. Standardized definitions for ICU readmission and death after ICU discharge could reduce the heterogeneity of pooled measures of association. Second, the study involved data linkages from multiple clinical and administrative data repositories. The analyses are contingent on the variables and quality of data recorded, which for the primary repository for our study has been reported to be of high quality.[24] Finally, this study was performed in a single healthcare system. It is possible that other systems may vary in risk factors associated with either outcome. However, the literature synthesis was not restricted in its scope and the identified risk factors were those commonly associated with either outcome. The novel approach of applying literature-based coefficients to prediction models should be generalizable to other outcomes and settings.

Conclusion

Using systematic review and meta-analysis to identify consistently associated risk factors to inform risk predictions models is feasible in critical care. The high sensitivity and negative predictive value in the tested models suggest that such models could be

used to facilitate early discharge planning in low-risk patients given the vast majority of predictors are static. Conversely, identifying high-risk patients remains challenging. New strategies, such as machine learning, need to be considered in order to more accurately derive and identify those patients at high risk of ICU readmission and death after ICU discharge.

Abbreviations

APACHE, Acute Physiology and Chronic Health Evaluation; AUROC, area under the receiver operating characteristics; CI, Confidence interval; DAD, Discharge Abstract Database; ICU, intensive care unit; IQR, interquartile range; OR, odds ratio; PRISMA, Preferred Reporting for Systematic Reviews and Meta-Analyses; SCM, Sunrise Clinical Manager.

Declarations

Ethics approval and consent to participate: This study was approved by the Conjoint Research Ethics Board (CHREB) at the University of Calgary (REB16-1263). Consent to participate was waived owing to the study design.

Consent for publication: Not applicable.

Availability of data and materials: The data that support the findings of this study are available from Alberta Health Services but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available.

Authors' contributions:

JMB: Conceptualization, Methodology, Formal analysis, Investigation, Validation, Writing – Original Draft, Writing – Review & Editing, Visualization, Project Administration

MTJ: Conceptualization, Methodology, Resources, Validation, Writing Review & Editing, Supervision

DJZ: Conceptualization, Methodology, Resources, Investigation, Validation, Writing Review & Editing, Supervision

HTS: Conceptualization, Methodology, Resources, Investigation, Validation, Writing Review & Editing, Supervision

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Figures

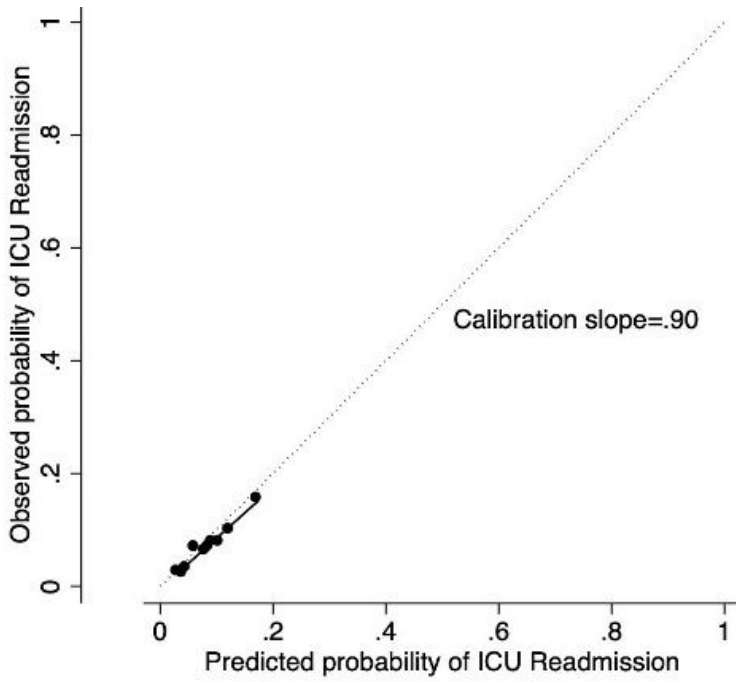


Figure 1

Calibration Slopes - ICU Readmission – Literature Weighted Model Performance

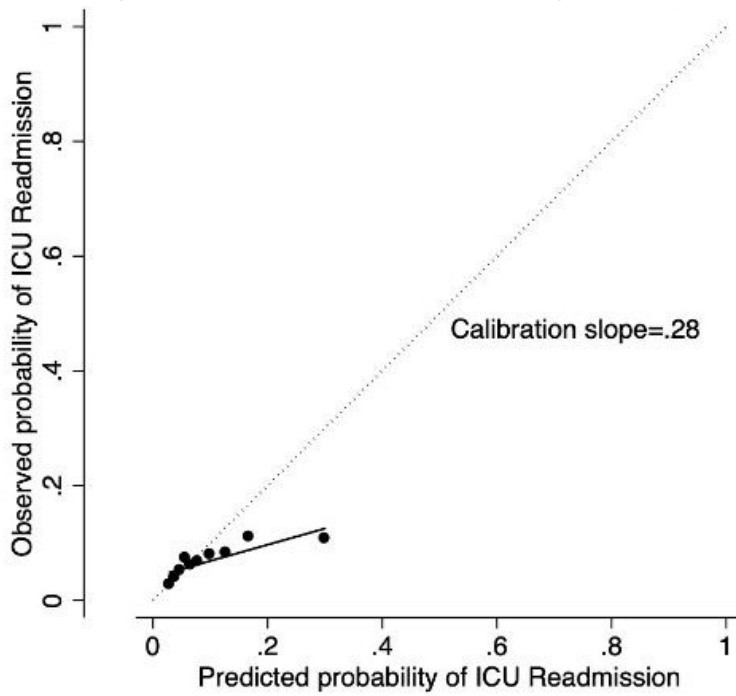


Figure 2

Calibration Slopes - ICU Readmission – Local Data Weighted Model Performance

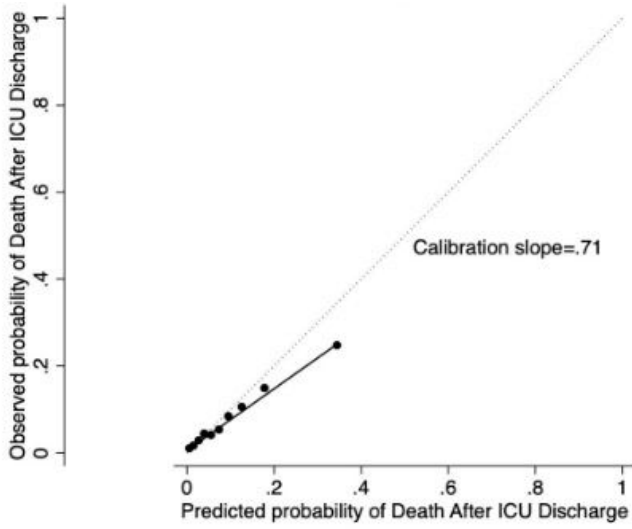


Figure 3

Calibration Slopes - Death After ICU Discharge – Literature Weighted Model Performance

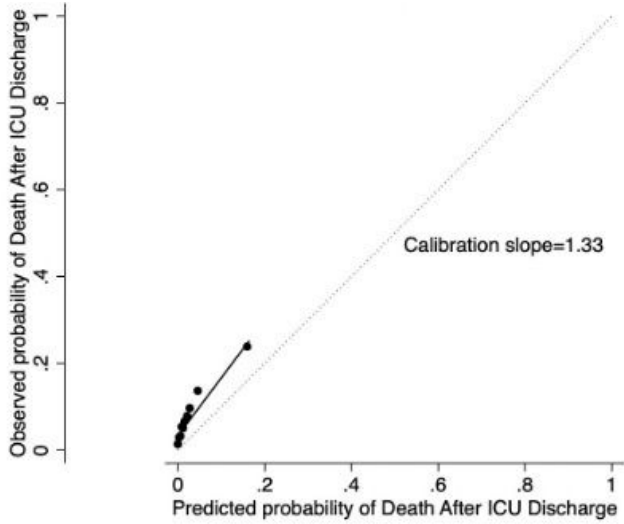


Figure 4

Calibration Slopes - Death After ICU Discharge – Local Data Weighted Model Performance

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