Because the focus of this analysis was to develop accurate mortality prediction equations on mechanically ventilated patients undergoing critical care interventions, we analyzed patients who required mechanical ventilation ≥2 days after ICU entry, which was identified from the corresponding codes. Non-invasive positive pressure ventilation was not included in analysis.

Development of the prediction model and potential risk factors

We utilized a split-half approach to prediction model development, using data from 2008 as the test dataset and data from 2009 and 2010 as the validation datasets. The primary measure used was in-hospital mortality. The in-hospital mortality prediction equation was constructed using the test dataset and evaluated using the validation datasets. Coefficients obtained from the test dataset were applied to cases in the validation datasets to calculate the predicted mortality.

Model development was based on up to 9 variables (Table 1). Age was used as a continuous variable. To determine the reason for ICU entry, patients who underwent surgery on the first ICU day were considered to be surgical cases. In these cases, patients who had both emergency hospital admission and underwent surgery on the day of hospital admission or the following day were defined as emergency surgical cases, whereas those who did not undergo emergency surgery were defined as elective surgical cases. All other patients were considered to be medical cases. To define admission categories, items in the administrative database pertaining to the course of admission were used. The emergency admission category indicates hospital admission after transport by ambulance or an unexpected admission. Organ failure was identified according to the study conducted by Angus et al [17]. The DPC system in Japan utilizes the International Classification of Diseases, 10th Revision (ICD-10) coding, rather than ICD-9 CM or ICD-10 AM, and ICD-10 AM codes were therefore translated to ICD-10 codes for identification of primary diagnosis and organ failure (Table 2). Charlson score is a clinical comorbidity index that predicts the 10 year survival

for a patient based on a range of comorbid conditions (e.g., heart disease, cancer, and liver disease). The score can be calculated from ICD codes available from administrative data, and increasing scores have been shown to have strong associations with mortality [18, 19].

Renal replacement therapy and pressors/vasoconstrictors were included in the candidate variables due to their reported association with 28-day hospital mortality in a previous study [20]. Renal replacement therapy included continuous renal replacement therapy, intermittent renal replacement therapy, plasma absorption, and plasma exchange, but excluded peritoneal dialysis due to its rare utilization for ICU patients. Pressors/vasoconstrictors included dopamine, dobutamine, norepinephrine, epinephrine, and vasopressin, but excluded the use of epinephrine in cardiopulmonary resuscitation. We were unable to distinguish whether dopamine was given as a low (renal) dose or for cardiovascular support, but found no evidence to support the possibility that low-dose dopamine was used [21]. We therefore assumed that dopamine was used for cardiovascular support.

Relationships between the individual candidate variables and in-hospital mortality were analyzed with χ-square tests or Student t-tests using the test dataset, depending on the type of data. After exclusion of variables with $p > 0.25$, the remaining variables were subjected to multiple logistic regression analyses (stepwise backward selection method). The model was constructed using variables with $p < 0.05$, and the C-statistics were calculated. Three models were developed: Model 1 included independent variables of demographics and clinical factors, and Model 2 included independent variables of procedures and therapies administered at any time during ICU admission (in addition to the variables in Model 1).

Prediction model performance

Calibration of the model was evaluated using the Hosmer-Lemeshow χ-square test. A

well-calibrated model has a low χ-square value (<15.5; df=8) and a high P value (>0.05). The discrimination of the model was assessed by the C-statistics, for which a value 0.9-1.0 was determined to represent high accuracy, 0.7-0.9 moderate accuracy, and 0.5-0.7 low accuracy.

Prediction model validation

The mortality prediction equation was cross-validated using the validation datasets to demonstrate the predictive validity of the prediction equation obtained from multiple logistic regression analysis of the test dataset. Coefficients derived from analysis of the test dataset were applied to the validation dataset in order to calculate predicted mortality. The performance of the equation was tested using the C-statistics (95% confidence interval [CI]) for the validation datasets from 2009 and 2010. All statistical analyses were performed using SPSS 18.0J (SPSS Inc., Chicago, IL).

RESULTS

The final samples for analysis from 2008, 2009 and 2010 comprised of the following: the numbers of hospitals per year were 282, 310 and 364, respectively; numbers of ICU patients were 38,625, 71,243 and 49,230, respectively; numbers of ventilated patients were 5,807, 10,610, and 7,576, respectively. The incidence of mechanically ventilated patients in ICU entry was approximately 15% for all three years. The details of patient characteristics for the sample are shown in Table 3. Preliminary univariate analyses showed significant differences between survivors and non-survivors in all patient characteristics except for gender in the three study years. In 2008 (test dataset), intracranial haemorrhage was the most frequent condition in the diagnostic category for non-survivors (10.4 %), while myocardial ischemia was the most frequent condition for survivors (13.2 %). All patient characteristics (excluding gender) were thus included as

independent variables in the consequent multiple logistic analysis.

Coefficients of the variables, odds ratios (OR), and 95% CIs are shown in Table 4. Factors associated with a high risk of death in Models 1 and 2 were hemopoietic malignancy (OR = 4.92, 95% CI = 2.15-11.24) and lung malignancy (OR = 6.00, 95% CI = 3.41-10.55), respectively. The Hosmer-Lemeshow χ-square values (P values) in Models 1 and 2 were 11.9 (0.15) and 15.6 (0.05), respectively; the models' C-statistics (95% CI) in the test dataset were 0.70 (0.69-0.72) and 0.78 (0.77-0.79), respectively (Table 5). Applying the final equation to the validation dataset showed similar discrimination when compared with that of the test dataset.

DISCUSSION

In this study, we developed and validated in-hospital mortality prediction equations in mechanically ventilated patients using data from Japan; we showed moderate discrimination in a model using patient demographics, clinical factors, and procedures administered during the ICU admission (Model 2). Mechanically ventilated patients in the ICU are frequently the subjects of epidemiological studies [22- 24]. The risk-adjustment methods previously employed in these studies frequently include APACHE, MPM and SAPS [25-36], but these methods are primarily dependent on organ scores that require physiological data. Ohno-Machado et al. obtained C-statistics for mortality prediction models using APACHE-II, APACHE-III, MPM_0, MPM_{24}, $MPM\text{-}II_0$, $MPM\text{-}II_{24}$, SAPS, and SAPS-II; and found that these all had C-statistics ≥ 0.8, except for SAPS [25]. In contrast to these models, Duke et al. [8] derived the COPE model using solely administrative data. This model has advantages in that it can predict mortality with relatively few variables from routinely-available data with relatively few variables from routinely-available data. The COPE model also includes mechanical ventilation as intensive care therapy, which has been shown to be strongly associated with hospital mortality. Therefore, for an analysis focusing on

mechanically ventilated patients using DPC data, there was a need to develop a new robust mortality prediction tool that did not include the independent variable of mechanical ventilation. In addition, because these models were developed specifically using Japanese data, and because of the ability of the DPC database to identify the details of medical care for mechanically ventilated patients in a uniform format from numerous hospitals, this approach has the capacity to support comparative evaluations of ICU performance using multicenter analysis in Japan.

Model 2 from our analysis may serve as a possible alternative model due to displaying moderate accuracy in the C-statistics. If the prognoses of mechanically ventilated patients are to be required, the use of existing scoring systems using physiological data may be more useful. But the intended applications of this equation (Model 2) lie in the retrospective evaluations of ICU performance in a multicenter analysis based on the identical format of DPC data introduced in 2004 in Japan.

The prediction equation in this study has the following advantages over existing models: the variables used in our equation utilize information that can be routinely obtained from administrative data. These variables are input by doctors and nurses in a timely manner on a daily basis rather than at or after discharge, which ostensibly improves the reliability of the data. Also, the model uses only 8 variables, which facilitates its generalizability and application. However, there is also the risk of coding errors, especially in ICU patients [8].

There are several limitations in the present study. First, we did not compare our model with scoring systems using physiological data, since our data did not include severity scores. Therefore, we cannot determine the relative accuracy of the model compared with other systems. Second, the administrative data include information on a "calendar day" basis, rather than an hourly basis, and therefore the first ICU day was defined by a calendar day. This provides no distinction regarding the use of renal replacement therapy and pressors/vasoconstrictors before or after ICU entry on the first ICU day. However, these resources are mostly used under monitoring in the ICU. Third, the

indications for renal replacement therapy and pressors/vasoconstrictors varied among the hospitals, which may have resulted in therapeutic bias. Fourth, the administrative data do not indicate if renal replacement therapy was given for chronic or acute renal failure, or for a non-renal indication; or if pressors/vasoconstrictors were used to treat hypovolemic or septic shock. Fifth, different admission criteria among the ICUs could have produced a selection bias that affected mortality. Our model has a therapeutic bias similarly to that of the COPE model, including the use of mechanical ventilation, renal replacement therapy, and pressors/vasoconstrictors. However, it is likely that there is little if any inappropriate application of these therapies due to ethical considerations. Finally, since our study sample included approximately 30 % of all ICUs in Japan, and did not include university hospitals and non-teaching hospitals, further verification and modification of the model may be required in a larger sample of patients and ICUs from a greater variety of hospital types.

The absence of physiological data is disadvantageous since diagnosis is not possible, but our model has the additional advantage in that it uses administrative data routinely collected for all patients with a high level of accuracy. Comparison of ICU performance using administrative data has applications for benchmarking and quality improvement, and our model establishes a method for the comparative evaluation of ICU performance.

Conclusions

The hospital mortality prediction equation for mechanically ventilated patients in intensive care proposed in this study is based solely on administrative data, and uses a relatively small number of variables that can be easily collected. In addition to the COPE model, Model 2 can be used to evaluate illness severity of mechanically ventilated patients based on administrative data and may be applicable to future critical care studies.

REFERENCES

1. Kuzniewicz MW, Vasilevskis EE, Lane R, Dean ML, Trivedi NG, Rennie DJ, Clay T, Kotler PL, Dudley RA. Variation in ICU risk-adjusted mortality: Impact of methods of assessment and potential confounders. CHEST. 2008; 133: 1319–1327.
2. McMillan TR, Hyzy RC. Bringing quality improvement into the intensive care unit. Crit Care Med. 2007; 35 [Suppl.]: S59–S65.
3. Leary T, Ridley S, Burchett K, Kong A, Chrispin P, Wright M. Assessing critical care unit performance: a global measure using graphical analysis. Anaesthesia. 2002; 57: 751–755.
4. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. An evaluation of outcome from intensive care in major medical centers. Ann Intern Med. 1986; 104: 410–418.
5. Knaus WA, Wagner DP, Zimmerman JE, Draper EA. Variations in hospital mortality and length-of-stay from intensive care. Ann Intern Med 1993; 118: 753–761.
6. Zimmerman JE, Shortell SM, Rousseau DM, et al. Improving intensive care. Crit Care Med 1993; 21: 1443–1451.
7. Render ML, Welsh DE, Kollef M, Lott JH 3rd, Hui S, Weinberger M, Tsevat J, Hayward RA, Hofer TP. Automated computerized intensive care unit severity of illness measure in the Department of Veterans Affairs: Preliminary results. Crit Care Med 2000; 28: 3540–3546.
8. Duke GJ, Santamaria J, Shann F, Stow P, Pilcher D, Ernest D, George C. Critical care outcome prediction equation (COPE) for adult intensive care. Crit Care Resusc 2008; 10: 35–41.
9. Curtis JR, Cook DJ, Wall RJ, Wall RJ, Angus DC, Bion J, Kacmarek R, Kane-Gill SL, Kirchhoff KT, Levy M, Mitchell PH, Moreno R, Pronovost P, Puntillo K. Intensive care unit quality improvement: A "how-to" guide for the interdisciplinary team. Crit Care Med 2006; 34: 211–218.

10. de Vos M, Graafmans W, Keesman E, Westert G, van der Voort PH. Quality measurement at intensive care units: which indiucators should we use? J Crit Care 2007; 22: 267–274.
11. Terblanche M, Adhikari NK. The evolution of intensive care unit performance assessment. J Crit Care 2006; 21: 19–22.
12. Lin YF, Ko WJ, Chu TS, Chen YS, Wu VC, Chen YM, Wu MS, Chen YW, Tsai CW, Shiao CC, Li WY, Hu FC, Tsai PR, Tsai TJ, Wu KD ; NSARF Study Group. The 90-day mortality and the subsequent renal recovery an critically ill surgical patients requiring acute renal replacement therapy. Am J Surg 2009; 198: 325–332.
13. Brar H, Olivier J, Lebrun C, Gabbard W, Fulop T, Schmidt D. Predictors of mortality in a cohort of intensive care unit patients with acute renal failure receiving continuous renal replacement therapy. Am J Med Sci 2008; 335: 342–347.
14. Soubrier S, Leroy O, Devos P, Nseir S, Georges H, d'Escrivan T, Guery B. Epidemiology and prognostic factors of critically ill patients treated with hemodiafiltration. J Crit Care 2006; 21: 66–72.
15. Pinsky MR. Hemodynamic evaluation and monitoring in the ICU. Chest 2007; 132: 2020–2029.
16. Lundberg GD. Practice parameter for the use of fresh-frozen plasma, cryoprecipitate, and platelets. JAMA 1994; 271: 777–781.
17. Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR. Epidemiology of severe sepsis in the United States: Analysis of incidence, outcome, and associated costs of care. Crit Care Med 2001; 29: 1303–1310.
18. Deyo R, Cherkin D, Ciol M. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. J Clin Epidemiol 1992; 45: 613–619.
19. Sundararajan V, Henderson T, Perry C, Muggivan A, Quan H, Ghali WA. New ICD-10

version of the Charlson Comorbidity Index predicted in-hospital mortality. J Clin Epidemiol 2004; 57: 1288–1294.

20. Umegaki T, Sekimoto M, Hayashida K, Imanaka Y. An outcome prediction model for adult intensive care. Crit Care Resusc 2010; 12: 96–103.
21. Dunning J, Khasati N, Barnard J. Low dose (renal dose) dopamine in the critically ill patient. Interact Cardiovasc Thorac Surg 2004; 3: 114–117.
22. Kim IB, Fealy N, Baldwin I, Bellomo R. A pilot study of the epidemiology and associations of pulse pressure variation among non-cardiac surgery critically ill patients. Crit Care Resusc 2011; 13: 156–61.
23. Lombardi R, Nin N, Lorente JA, Frutos-Vivar F, Ferquson ND, Hurtado J, Apeztequia C, Desmery P, Raymondos K, Tomicic V, Cakar N, González M, Elizalde J, Nightingale P, Abrouq F, Jibaja M, Arabi Y, Moreno R, Matamis D, Anzueto A, Esteban A; VENTILA Group. An assessment of the Acute Kidney Injury Network creatinine-based criteria in patients submitted to mechanical ventilation. Clin J Am Soc Nephrol 2011; 6: 1547–1555.
24. Peñuelas O, Frutos-Vivar F, Fernández C, Anzueto A, Epstein SK, Apeztequía C, González M, Nin N, Raymondos K, Tomicic V, Desmery P, Arabi Y, Pelosi P, Kuiper M, Jibaja M, Matamis D, Ferquson ND, Esteban A; Ventila Group. Characteristics and outcomes of ventilated patients according to time to liberation from mechanical ventilation. Am J respire Crit Care Med 2011; 184: 430–437.
25. Ohno-Machado L, Resnic FS, Matheny ME. Prognosis in critical care. Annu Rev Biomed Eng 2006; 8: 567–599.
26. Rosenberg AL. Recent innovations in intensive care unit risk-prediction models. Curr Opin Crit Care 2002; 8: 321–330.
27. Afessa B, Gajic O, Keegan MT. Severity of illness and organ failure assessment in adult

intensive care units. Crit Care Clin 2007; 23: 639–658.

28. Cook DA. Methods to assess performance of models estimating risk of death in intensive care patients: a review. Anaesth Intensive Care 2006; 34: 164–175.
29. Junger A, Engel J, Benson M, Hartmann B, Röhriq R, Hempelmann G. Risk predictors, scoring systems and prognostic models in anesthesia and intensive care. Part II. Intensive Care. Anasthesiol Intensivmed Notfallmed Schmerzther 2002; 37: 591–599.
30. Schusterschitz N, Joannidis M. Predictive capacity of severity scoring systems in the ICU. Contrib Nephrol 2007; 156: 92–100.
31. Kramer AA. Predictive mortality models are not like fine wine. Crit Care 2005; 9: 636–637.
32. Chen FG, Khoo ST. Critical care medicine: a review of the outcome prediction in critical care. Ann Acad Med Singapore 1993; 22: 360–364.
33. Harrison DA, D'Amico G, Singer M. Case mix, outcome, and activity for admissions to UK critical care units with severe acute pancreatitis: a secondary analysis of the ICNARC Case Mix Programme Database. Crit Care 2007; 11: S1.
34. Strand K, Flaatten H. Severity scoring in the ICU: a review. Acta Anaesthesiol Scand 2008; 52: 467–478.
35. Capuzzo M, Moreno RP, Le Gall JR. Outcome prediction in critical care: the Simplified Acute Physiology Score models. Curr Opin Crit Care 2008; 14: 485–490.
36. Duke GJ, Piercy M, DiGiantomasso D, Green JV. Comparison of intensive care outcome prediction models based on admission scores with those based on 24-hour data. Anaesth Intensive Care 2008; 36: 845–849.

Table 1 Candidate variables used to develop the in-hospital mortality prediction equation

Type	Candidate variables	Categories
Demographics	(1) Age (years)	Continuous variable
	(2) Gender	Male, Female
Clinical factors	(3) Hospital admission course	Scheduled*, Emergency
	(4) Primary diagnosis on admission	(See Table 2)
	(5) Reason for entering ICU	After elective surgery*, After emergency surgery, Medical disease
	(6) Charlson score	0*, 1, 2, 3, ≥ 4
	(7) Number of organ failures (except for respiratory failure)	0*, ≥ 1
Procedures administered at any time during ICU admission	(8) Renal replacement therapy	Yes = 1, No = 0
	(9) Pressor/vasoconstrictor	Yes = 1, No = 0

* Reference category for hospital mortality prediction

Table 2 Recoding of ICD-10 AM and ICD-9 CM codes to ICD-10 codes

Diagnostic category	ICD-10 AM	ICD-10	Diagnostic category	ICD-9 CM	ICD-10
Hemopoietic malignancy	C80-99	C81-96	Cardiovascular dysfunction		
Penetrating trauma	T15-19	T15-19	Shock without trauma	785.5	A419
Other central nervous system disease	G9	G9			A483
Cardiac arrest	I46	I46			R570
Aplastic anemia	D6	D60-61			R571
Protozoal sepsis	B50-64	B50-64			R578
Hemorrhagic shock	R57-58	R57-58			R579
Secondary malignancy	C76-79	C76-80	Hypotension	458	I959
Stroke or cerebrovascular accident	I63-64	I63-64	Neurologic dysfunction		
Interstitial lung disease	J8	J8	Encephalopathy	348.3	F058
Liver disease	K7	K7			G934
Bacterial sepsis	A4	A4			G938
Lung malignancy	C3	C3			I672
Intracranial hemorrhage	I60-62	I60-62			I674
Anemia	D5	D5			I678
Central nervous system malignancy	C69-72	C69-72			
Pulmonary vascular	I26-28	I26-28			K729
Fungal sepsis	B30-49	B35-49			K868
Renal failure	N1	N17-N19			G948
Ischemic bowel	K55	K55	Transient organic psychosis	293	F069
Gastrointestinal investigation	R1	R1	Anoxic brain damage	348.1	G931
Environmental disease	T66-79	T66-78	Hematologic dysfunction		
Breast cancer	C5	C5	Secondary thrombocytopenia	287.4	D695
Malignancy, other	D37-49	D37-48	Thrombocytopenia, unspecified	287.5	D696
Pneumonia	J1	J12-18	Other/unspecified coagulation defect	286.9	D65
Pneumoconiosis	J60-79	J60-J70	Defibrination syndrome	286.6	D65
Head injury	S0	S0	Hepatic dysfunction		
Pancreatic cancer	C22-26	C25	Acute and subacute necrosis of liver	570	K729
Type 2 diabetes	E11	E11	Hepatic infarction	573.4	K763
Cardiac arrhythmias	I49	I47-49	Renal dysfunction		
Fluid and electrolyte disorders	E86-88	E86-88	Acute renal failure	584	N179
Enteritis or colitis	K50-52	K50-52			
Other intestinal disease	K63	K63			
Respiratory failure	J95-99	J96			
Lower limb trauma	S7	S7			
Other cerebrovascular disease	I65-69	I65-69			
Chronic obstructive pulmonary disease	J40-44	J40-44			
Malabsorption	K9	K90			
Drug poisoning	T36-50	T36-50			
Epilepsy	G4	G40			
Cardiac failure	I22-25	I50			
Myocardial ischemia	I20	I20-25			
All other diagnoses*					

Table 3 Patient characteristics in 2008, 2009, and 2010

	2008			2009			2010		
	Survivors (n = 4,002)	Non-survivors (n = 1,805)	P value	Survivors (n = 7,056)	Non-survivors (n = 3,554)	P value	Survivors (n = 5,234)	Non-survivors (n = 2,342)	P value
(1) Age (Years)	68.0(13.6)	71.8(12.8)	<0.01**	68.8(13.7)	72.5(13.3)	<0.01**	67.9(14.2)	72.0(13.0)	<0.01**
(2) Gender (Male)	62.5	62.9	0.76	61.6	62.6	0.29	62.9	62.7	0.91
(3) Hospital admission course (Emergency)	64.8	84.3	<0.01**	68.2	84.7	<0.01**	57.5	72.3	<0.01**
(4) Primary diagnosis on admission									
Hemopoietic malignancy	0.2	1.2		0.3	1.8		0.2	1.5	
Penetrating trauma	0.1	0.1		0.1	0.1		0	0.1	
Other central nervous system disease	0.6	1.6		0.4	1.1		0.3	1.3	
Cardiac arrest	0	0		0	0		0	0	
Aplastic anemia	0	0.1		0	0.1		0	0.1	
Protozoal sepsis	0	0.1		0	0		0.1	0.2	
Hemorrhagic shock	0.3	0.2		0.3	0.6		0.2	0.3	
Secondary malignancy	0.6	0.7		0.4	0.4		0.5	0.7	
Stroke or cerebrovascular accident	1.5	2.5	<0.01**	1.5	2.6	<0.01**	1.5	2.4	<0.01**
Interstitial lung disease	1.2	2.4		1.2	3.6		1.1	3.2	
Liver disease	0.1	0.3		0.2	0.8		0.2	0.6	
Bacterial sepsis	1.5	2.9		1.7	2.9		1.5	3.5	
Lung malignancy	2.9	1.7		0.9	1.5		1.1	1.4	
Intracranial hemorrhage	5.1	10.4		5.6	9.8		5.4	8.5	
Anemia	0	0.1		0.1	0.1		0.1	0.1	
Central nervous System malignancy	0.1	0.2		0.1	0.1		0.2	0.3	
Pulmonary vascular	0.3	0.2		0.4	0.5		0.6	0.3	
Fungal sepsis	0	0.1		0.1	0.2		0	0.3	

Renal failure	0.9	1.3		0.8	1.3		0.6	1.7	
Ischemic bowel	0.3	0.7		0.3	0.4		0.2	0.3	
Gastrointestinal investigation	0.2	0.3		0.2	0.2		0.1	0.3	
Environmental disease	0.2	0.5		0.1	0.3		0.5	0.6	
Breast cancer	0.2	0.4		0.3	0.2		0.3	0.3	
Malignancy-other	0.4	0.6		0.4	0.5		0.7	0.7	
Pneumonia	2.4	4.8		2.5	4.8		2.4	4.5	
Pneumoconiosis	1	2.3		1.5	2.1		1.4	2	
Head injury	1.4	3		1.3	2.1		1.3	2.6	
Pancreatic cancer	0.2	0.1		0.4	0.4		0.3	0.6	
Type 2 diabetes	0.1	0.1		0.2	0.2		0.1	0.2	
Cardiac arrhythmias	0.8	1.1		0.8	0.8		1	0.9	
Fluid and electrolyte disorders	0.2	0.3		0.2	0.5		0.4	0.5	
Enteritis or colitis	0	0.2		0.1	0.1		0.2	0	
Other intestinal disease	0.7	0.7		0.8	1		0.8	0.7	
Respiratory failure	1.6	2.9		2	2.6		1.9	2.2	
Lower limb trauma	0.3	0		0.5	0.7		0.4	0.6	
Other cerebrovascular disease	1.2	0.4		1.1	0.3		1.3	0.5	
Chronic obstructive pulmonary disease	0.4	0.3		0.4	0.3		0.6	0.5	
Malabsorption	0	0		0	0		0	0	
Drug poisoning	0.8	0.1		0.8	0.1		0.9	0	
Epilepsy	0.3	0.1		0.4	0.1		0.4	0.1	
Cardiac failure	9.1	6.1		9.9	6.7		10.1	6.2	
Myocardial ischemia	13.2	8.6		12.5	7.4		12.6	6.7	
(5) Reason for entering ICU									
After emergency surgery	19.9	21.6	<0.01**	20	20.5	<0.01**	18.2	50.8	<0.01**
Internal medical disease	53.7	72		55.2	72.9		18.4	71.4	
(6) Charlson score									

1	29.2	26		31	26.9		31.4	25	
2	15.8	15.9	<0.01**	17.6	18.1	<0.01**	17.3	17.4	<0.01**
3	6.4	9.1		7.6	8.7		7.7	9.9	
≥4	3	4.9		3.6	4.9		3.6	6.6	
(7) Number of organ failures (except for respiratory failure) ≥1	28.5	47.1	<0.01**	32.8	51.9	<0.01**	32.4	55.7	<0.01**
(8) Renal replacement therapy	10.9	28.1	<0.01**	10.3	28.6	<0.01**	10.3	32.4	<0.01**
(9) Pressors/vasoconstrictors	73.2	88.3	<0.01**	71.4	88.9	<0.01**	70	88.1	<0.01**

Continuous variables presented as mean(SD); Categorical variables presented as percentage;
* $p < 0.05$, ** $p < 0.01$

Table 4 Variable coefficients used in the hospital mortality prediction models

	Model 1		Model 2	
Variable	B	OR (95% CI)	B	OR (95% CI)
(1) Age (Years)	0.02	1.02 (1.02 – 1.03)	0.02	1.02 (1.02 – 1.03)
(3) Hospital admission course				
Emergency	0.33	1.39 (1.12 – 1.72)	0.48	1.61 (1.28 – 2.01)
(4) Primary diagnosis on admission				
Hemopoietic malignancy	1.59	4.92 (2.15 – 11.24)	1.78	5.90 (2.51 – 13.90)
Other central nervous system disease	0.65	1.91 (1.08 – 3.36)	0.99	2.69 (1.49 – 4.85)
Stroke or cerebrovascular accident			0.81	2.25 (1.46 – 3.45)
Interstitial lung disease			0.77	2.16 (1.37 – 3.40)
Bacterial sepsis				
Lung malignancy	0.96	2.62 (1.49 – 4.58)	1.79	6.00 (3.41 – 10.55)
Intracranial hemorrhage	0.42	1.53 (1.20 – 1.95)	1.53	4.64 (3.61 – 5.96)
Pneumonia			0.63	1.88 (1.34 – 2.64)
Pneumoconiosis			0.84	2.32 (1.43 – 3.78)
Head injury	0.46	1.58 (1.06 – 2.37)	1.45	4.26 (2.79 – 6.52)
Respiratory failure			0.69	1.99 (1.32 – 2.99)
Drug poisoning	-1.99	0.14 (0.03 – 0.58)		
Cardiac failure	-1.06	0.35 (0.27 – 0.44)	-0.65	0.52 (0.41 – 0.67)
Myocardial ischemia	-0.59	0.55 (0.44 – 0.69)	-0.36	0.70 (0.56 – 0.86)
(5) Reason for entering ICU				
After emergency surgery	1.02	2.77 (2.03 – 3.79)	0.71	2.04 (1.47 – 2.83)
Medical disease	1.32	3.76 (2.86 – 4.94)	1.25	3.50 (2.63 – 4.66)
(6) Charlson score				
3	0.46	1.58 (1.26 – 1.98)	0.36	1.44 (1.13 – 1.83)
≥4	0.61	1.84 (1.35 – 2.50)	0.44	1.56 (1.12 – 2.16)
(7) Number of organ failures (except for respiratory failure) ≥1 (%)			0.63	1.88 (1.64 – 2.15)
(8) Renal replacement therapy (%)			1.05	2.86 (2.42 – 3.36)
(9) Pressors/vasoconstrictors (%)			1.27	3.55 (2.95 – 4.26)
Constant	-3.49		-5.41	

B: β coefficient; OR: Odds Ratio; CI: confidence interval
Predicted mortality risk = $e^y / (e^y + 1)$, where $y = B_{(1)} * (1) + B_{(3)} * (3) + B_{(4)} * (4) + B_{(5)} * (5) + B_{(6)} * (6) + B_{(7)} * (7) + B_{(8)} * (8) + B_{(9)} * (9) + \text{constant}$.
(1), (3), (4), (5), (6), (7), (8), and (9) = 1 if variables are applicable and 0 if variables are not applicable.

Table 5 Model discrimination for the mortality prediction equation in test and validation datasets

Model 1	2008 (test)	0.70	0.69 - 0.72
	2009 (validation)	0.69	0.68 - 0.70
	2010 (validation)	0.70	0.69 - 0.71
Model 2	2008 (test)	0.78	0.77 - 0.79
	2009 (validation)	0.78	0.77 - 0.79
	2010 (validation)	0.79	0.78 - 0.80

Journal of Anaesthesiology Clinical Pharmacology
Official publication of the Research Society of Anaesthesiology Clinical Pharmacology
Home Current issue Instructions Submit article

J Anaesthesiol Clin Pharmacol. 2011 Apr-Jun; 27(2): 180–184. PMCID: PMC3127295
doi: 10.4103/0970-9185.81816

The impact of acute organ dysfunction on patients' mortality with severe sepsis

Takeshi Umegaki, Hiroshi Ikai, and Yuichi Imanaka

Department of Healthcare Economics and Quality Management, Kyoto University Graduate School of Medicine, Yoshida Konoe-cho, Sakyo-ku, Kyoto 606 - 8501, Japan

Address for correspondence: Prof. Yuichi Imanaka, Department of Healthcare Economics and Quality Management, Kyoto University Graduate School of Medicine, Kyoto, Japan. E-mail: imanaka-y@umin.net

Abstract

Background:

Severe sepsis leads to organ failure and results in high mortality. Organ dysfunction is an independent prognostic factor for intensive care unit (ICU) mortality. The objective of the present study was to determine the effect of acute organ dysfunction for ICU mortality in patients with severe sepsis using administrative data.

Materials and Methods:

A multicenter cross-sectional study was performed in 2008. The study was conducted in 112 teaching hospitals in Japan. All cases with severe sepsis in ICU were identified from administrative data.

Results:

Administrative data acquired for 4196 severe septic cases of 75,069 cases entered in the ICU were used to assess patient outcomes. Cardiovascular dysfunction was identified as the most major organ dysfunction (73.0%), and the followings were respiratory dysfunction (69.4%) and renal dysfunction (39.0%), respectively. The ICU mortality and 28-day means 28-day from ICU entry. were 18.8% and 27.7%, respectively. After adjustment for age, gender, and severity of illness, the hazard ratio of 2, 3, and ≥4, the organ dysfunctions for one organ failure on ICU mortality was 1.6, 2.0, and 2.7, respectively.

Conclusions:

We showed that the number of organ dysfunction was a useful indicator for ICU mortality on administrative data. The hepatic dysfunction was the highest mortality among organ dysfunctions. The hazard ratio of ICU death in severe septic patients with multiple organ dysfunctions was average 2.2 times higher than severe septic patients with single organ dysfunction.

Keywords: Intensive care units, multicenter study, multiple organ failure, mortality, sepsis

Introduction

Severe sepsis is one of the leading causes of morbidity and high mortality in intensive care units (ICUs).[1] Septic patients had more severe organ dysfunction, longer intensive care unit and hospital lengths of stay, and higher mortality rate than patients without sepsis.[2,3]

There was a significant increase in ICU mortality with increasing number of organ dysfunction,[4] and administrative data have been used to perform the study on ICU research.[5–9] The aim of the present

study is to determine the effect of acute organ dysfunction for ICU mortality in patients with severe sepsis using the administrative data.

Material and Methods

Data source

Data were obtained from the Quality Indicator/Improvement Project, which collects administrative detailed claim data from acute care hospitals in Japan. In voluntary participating hospitals, 112 ICUs were included in 2009. Administrative data were comprised of clinical information and healthcare claim data. Clinical information included patient demographics, primary and secondary diagnoses, comorbidities at the time of and after admission, operative data, severity of illnesses, as well as any special treatments (i.e. radiation therapy, artificial respiration, chemotherapy). In contrast, healthcare claim data itemized the type, quantity, and fees for all tests, medications, procedures, use of intensive or specialized care, and nursing services.

Cases and selection criteria

The following selection criteria were used in the study: (i) primary diagnosis of sepsis (codes in the International Classification of Diseases, 10th version) [Table 1]; (ii) complication of acute organ dysfunction classified by Martin *et al.*;[5] and (iii) discharge date between January 1 and December 31st, 2009. We excluded less than 18-year old cases. In addition, we did not analyze metabolic dysfunction as acute organ dysfunction, since SOFA score, which was the general and principal indicator for evaluation of acute organ dysfunction in critically ill patients, did not include this item. We defined severe sepsis as fulfillment of (i) and (ii), as well as previous studies.[5,6]

Evaluation of cases

The patient characteristics were express by age, gender, severity of illness, acute organ dysfunction, admission course, reason for ICU entry, and underlying disease. We evaluated severity of illness using the Critical care Outcome Prediction Equation (COPE) model derived by Duke *et al.*, which has an area under the ROC curve of 0.83–0.84 and relatively few variables, and is the model based on administrative data alone.[10]

The intervention for severe septic patients was presented by mechanical ventilation, renal replacement therapy, use of catecholamine; dopamine, dobutamine, noradrenalin, and adrenaline including SOFA score.

Patient outcomes

The ICU mortality, 28-day mortality, hospital mortality, the length of ICU stay, and the length of hospital stay were evaluated. The ICU, 28-day, and hospital mortality rate was calculated by dividing the number of non-survivors following ICU discharge, day 28, and hospital discharge by the total number of severe septic cases, respectively.

Impact of ICU mortality on acute organ dysfunction

First, Kaplan–Meier curve was expressed for the association between the number of organ dysfunction ad ICU mortality. Log-rank statistics was performed on each factor. Second, Cox proportional hazard model was performed for unadjusted and adjusted evaluation of the effect of acute organ dysfunction on ICU mortality. We adjusted ICU mortality with age, gender, and severity of illness. In addition, impact of each organ dysfunction was assessed using hazards ratio.

Statistical analysis

All data are shown as means ± SD, or percentages. $P < 0.05$ was considered to be significant. All statistical analyses were performed using SPSS 11.0J (SPSS Inc., Chicago, IL). The Institutional Review Board of the Faculty of Medicine at the Graduate School of Medicine of Kyoto University, Japan, approved this study.

Results

The data used for this study was from 75,069 ICU patients discharged from 112 hospitals. Of these, 4252 (5.7%) were identified as severe septic cases, but only 56 (1.3%) matched the exclusion criteria, leaving 4196 (98.7%) that were included in our analysis.

Patient background is shown in Table 2. Over half of the patients were male (n =2575, 61.4%), and had internal medical disease caused without surgery as reason for ICU entry (n = 2562, 61.1%). Therapeutic intervention for severe septic patients was most commonly performed using mechanical ventilation (n = 2900, 69.1%), followed by dopamine use (n = 2726, 65.0%). Continuous renal replacement therapy, which was the most frequently used, was performed in 1080 cases (25.7%) of the patients performing renal replacement therapy.

Patient outcomes

The length of ICU stay was 7.5 days in severe septic patients. The ICU mortality in severe septic patients was 18.8%. However the hospital mortality was nearly 2.5 times higher than the ICU mortality, though the expected mortality using COPE model was 21.7%. The length of hospital stay was over a month in severe septic patients.

Cox proportional hazard model for ICU mortality on acute organ dysfunction

In our severe septic cases, 1582 patients (37.7%) had two organ dysfunction, and 3055 (72.8%) had multiple organ dysfunction. In patients with more than or equal to 4 organ dysfunctions, ICU mortality (38.9%) was over four times compared to single organ dysfunction (8.9%) [Table 3]. [Figure 1] showed a Kaplan-Meier curve calculating from ICU entry in each number of organ dysfunctions. After adjustment for age, gender, and severity of illness, the hazard ratio (HR) increased in increasing number of organ dysfunction (1.6, 2.0, and 2.7 in 2-, 3-, and ≥4 organ dysfunctions, respectively) [Table 3].

Majority of patients (n = 3065, 73.0%) had cardiovascular dysfunction, and following was respiratory dysfunction (n = 2194, 69.4%). Hepatic dysfunction was minority (n = 59, 1.4%), however, ICU mortality and hazard ratio with hepatic dysfunction was the most highest in other dysfunction (32.2% and 2.0, respectively). However, cardiovascular and neurologic dysfunctions were not significant factor for the ICU death (P = 0.178 and P = 0.703, respectively) [Table 4].

Discussion

Our best finding was the identification of the increasing hazard ratio of the increasing number of organ dysfunction for the death of ICU using administrative data, without respect to combination of organ dysfunctions. The hazard ratio of ICU death in severe septic patients with multiple organ dysfunctions was average 2.2 times higher than severe septic patients with single organ dysfunction. Mortality of severe sepsis patients is greater than 30%[1,11] and an important theme challenging improvement of patient outcomes such as surviving sepsis campaign.[12–15] Recently, it was shown that acute organ dysfunction was useful prognostic indicator for ICU mortality, especially that there was a significant increase in ICU mortality with increasing number of organ failures.[4,16] Such result was reported in the study for dogs.[17]

Cardiovascular dysfunction was strong factor in organ dysfunctions, and a number of organ dysfunctions were available for assessment of ICU death compared to SOFA score.[4] Hepatic dysfunction was the strongest factor for ICU death in this study. However, impact of ICU mortality on cardiovascular dysfunction was not significant for ICU death. Concerning cardiovascular dysfunction, our study and the report of N for *et al.*[4] was controversial. It might be caused by our subject of only severe sepsis or selection bias such as the variety during recording physicians under administrative data.

In this study, severe septic patients had ICU mortality of 18.8%, and 28-day mortality of 27.7%. Hospital mortality was very high (45.6%), and there was extreme difference between our hospital mortality and the