ORIGINAL ARTICLE

Epidemiology and Characteristics of Organ Failure and Support in the Medical Intensive Care Units: A Prospective Cohort Study

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Objective: The objectives are to explore the characteristics of organ failure and support in the medical intensive care units and exam the effect of organ failure on mortality.

Materials and Methods: This was a prospective cohort study of critically ill medical patients. All consecutive patients were collected for one year. Demographic data, organ failure characteristics, and support were recorded. Outcomes were mortality at day 28, 90, and year one.

Results: A total of 446 patients were included. The median age was 60 years (IQR 46, 73), and the male was 58.3%. Median Charlson comorbidities index was 4 points (IQR 2, 4). Median APACHE II and SOFA scores were 23 (IQR 18, 30) and 8 points (IQR 5, 11). Acute respiratory failure (ARF) developed 69.1% (95% CI 61.7 to 70.2). Mechanical ventilation duration was 6 days (95% CI 4 to 6), whereas the ventilator-free day on day 28 was 22 days (95% CI 16 to 23). Ventilator associated pneumonia rate was 9.4 events per 1,000 ventilator-days (95% CI 6.1 to 13.8). Acute kidney injury (AKI) developed 71.5% (95% CI 66.8 to 75.7): 25.2%, 20.5%, and 54.3% had stage I, II, III AKI. Patients developed shock 66.8%. Septic shock was the most common type. The median time to start nutrition support was 1 day (IQR 1.0, 2.0). Mortality at day 28, day 90, and 1 year were 30.7% (95% CI 26.6 to 35.1), 42.4% (95% CI 37.9 to 47), and 53.8% (95% CI 49.2 to 58.4). ARF had a constant effect on death at day 28 (HR 3.68, 95% CI 1.96 to 6.91). Shock had a peak effect on mortality since day 1 of ICU admission (HR 120.3, 95% CI 4.76 to 3,040.7) and still had a significant impact on day 28 (HR 2.07, 95% CI 1.14 to 3.74). Development of stage III AKI had an earlier effect than stage II AKI on mortality and a peak effect at day 28.

Conclusion: AKI and ARF were common in ICU. Shock had the highest effect on mortality, followed by ARF and AKI.

Keywords: Organ failure; Medical critically ill patients; Intensive care unit; Mortality; Epidemiology

J Med Assoc Thai 2023;106(Suppl.1):S36-45

Website: http://www.jmatonline.com

Multiple organ dysfunction is ubiquitous in intensive care units (ICU). Critically ill patients admitted to ICU mostly have at least one organ failure[1]. Therefore, critical care practitioners should early recognition and support failed organs. The consequences of organ failure, including shock, acute respiratory failure (ARF), and acute kidney injury (AKI), cause subsequent morbidity and mortality. Therefore, preventing further organ dysfunction and managing organ failure is a crucial objective.

Patients admitted to the ICU have heterogeneous diseases. Forty percent of patients have one comorbidity[2]. Most studies about organ failure are on specific organ dysfunction[3,4]. Moreover, the incidence of a specific type of organ failure depends on the ICU sub-specialties.

It is well established that organ failure numbers and severity are associated with mortality[5]. Although severity scores in the first 24 hours in ICU, such as the Acute Physiology and Chronic Health Evaluation (APACHE) and Simplified Acute Physiology Score (SAPS), can predict mortality, the magnitude of the effects of each failed organ is not well explored. Cardiovascular dysfunction has a higher likelihood of mortality compared to other organs[6]. However, the time-varying effects of organ failures are unknown. Limitation of ICU bed availability in countries with limited resources leads to more severe patients being admitted to the ICU. The epidemiological data of organ

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How to cite this article:

Panitchote A, Patjanasoontorn B, Phunmanee A, Pisprasert V, Rattanachaiwong S, Inpromma L, Samuksaman S, Bunsut P, Sriton J, Daungornnam J. Epidemiology and Characteristics of Organ Failure and Support in the Medical Intensive Care Units: A Prospective Cohort Study. J Med Assoc Thai 2023;106:S36-45.

DOI: 10.35755/jmedassocthai.2023.S01.13759

dysfunction and support in limited-resource countries is scanty.

The objectives of our study are to explore the epidemiology of organ failure and support in medical ICU and exam the time-varying effect of each type of organ dysfunction on mortality. The authors are interested in ARF, AKI, shock, and nutrition support.

Materials and Methods

Study setting and patient population

The authors conducted a prospective cohort study from June 1, 2014, to May 31, 2015, at the Srinagarind Hospital, Khon Kaen University, Thailand, a university academic center. The authors included all consecutive patients admitted to the ICU during that period. The study population had aged more than or equal to 16 years old. The authors excluded ICU readmission visits on the same hospitalization. Therefore, patients who were readmitted to the ICU were recorded data at the first ICU visit. The Khon Kaen University Ethics Committee for Human Research approved this study (Approval Number: HE571275). The Institutional Review Board waived informed consent because this study was a health-related registry and posed no more than minimal risks to participants.

Data collection and definition

Demographic data included: age, sex, body mass index (BMI), comorbidities, Charlson comorbidity index, the principal diagnosis of hospital admission based on the International Statistical Classification of Disease and Related Health Problems 10th Revision (ICD-10), the reason for ICU admission, and source of ICU admission. In addition, the severity of illness, including the sequential organ failure assessment (SOFA) score and the acute physiology and chronic health evaluation (APACHE) II score, were recorded on day 1 of ICU admission.

ARF was defined as patients receiving invasive mechanical ventilation or non-invasive ventilation (NIV) total duration of more than or equal to 24 hours[7-9]. Duration of mechanical ventilation and a ventilator-free day (VFD) at day 28 were recorded. Ventilator-associated events (VAE) definition and algorithm were defined following the Centers for Disease Control and Prevention's National Healthcare Safety Network. The VAE definition includes three subcategories: 1) Ventilator-Associated Condition (VAC); 2) Infection-related Ventilator-Associated Complication (IVAC); and 3) Possible VAP (PVAP)[10,11]. IVAC is potentially infectious, whereas PVAP is potentially pneumonia.

AKI and severity of AKI were defined according to the Kidney Disease Improving Global Outcomes (KDIGO) 2012 guidelines, using serum creatinine and urine output criteria[12]. The authors also recorded the mode and duration of renal replacement therapy (RRT). In addition, intake, output, and percentage of fluid overload were collected during the ICU stay. The percentage of fluid overload was calculated using the following formula[13]: Percentage of fluid overload (%) = [fluid intake – total output]/body weight at ICU admission (kg) x100.

Shock was defined as patients with mean arterial pressure <70 mmHg and signs of tissue hypoperfusion, including cyanosis, decreased urine output <0.5 mL/kg/hour, altered mental status, or serum lactate level >1.5 mmol/L[14]. Septic shock was defined following Surviving sepsis campaign: international guidelines 2012[15], which is sepsis patients who are hypotensive despite fluid resuscitation >30 mL/kg within 2 hours. Cardiogenic shock was defined as shock patients who had cardiac index ≤2.2 L/min/m^2 with evidence of cardiac dysfunction from echocardiography or pulmonary capillary wedge pressure ≥15 mmHg[16]. Obstructive shock was defined as obstruction of cardiopulmonary circulation[17] and adrenal shock was defined as caused by hypoadrenalism[18]. The authors also recorded the type and dose of vasopressors and inotropes.

One year vital status of patients discharged alive from the hospital was retrieved from the Thai population database of the Bureau of Registration Administration, Department of Provincial Administration, Ministry of the Interior.

Study data were collected and managed using REDCap electronic data capture tools hosted at Khon Kaen University[19,20].

Statistical analysis

Continuous covariates were reported in mean and standard deviation. However, non-normally distributed data were described as the median and interquartile range (IQR). The normality test was performed with the Shapiro-Wilk test. Categorical variables were presented in count and percentage. The authors compared the continuous and categorical covariates between survivors and non-survivors using Student's t-test or Mann-Whitney test and Chi-square test or Fisher exact test as appropriate. The authors reported 95% confidence interval (CI) of median using the bias-corrected and accelerated (BCa) bootstrap method (100,000 draws)[21,22].

Factors associated with time to death on day 28 after ICU admission were explored using univariable Cox proportional hazards regression. However, the authors tested the proportional hazard assumption with scaled Schoenfeld residuals. Variables with AKI, shock, and Charlson comorbidity index were treated as a time-varying covariate due to noncompliance with the proportional hazard assumptions. Types of organ failure associated with survival time at day 28 were analyzed with Royston-Parmar flexible

parametric survival with a time-varying covariate model. To identify the best model fit, the authors varied the degree of freedom used in the natural cubic spline function to model the baseline hazard function and the time-varying effect of AKI, shock, and comorbidity index. A combination of model-derived hazard plots and the Akaike information criterion was used to choose the model with the best fit for the final analysis. The model used 4 knots for the baseline and 1 knot for the time-dependent effect.

The analysis was performed using R version 4.2.1 (R Foundation for Statistical Computing, Vienna, Austria). The level of statistical significance was set at $p<0.05$ (two-tailed).

Results

There were 473 admissions to the medical intensive care units (ICU) in the Srinagarind Hospital, Khon Kaen, Thailand, over one year between June 1, 2014 and May 31, 2015. Patients who were readmitted to the MICU are 27 patients. Therefore, we included 446 patients for the analysis. Descriptive data of the cohort are shown in Table 1. The median patient age was 60 years (IQR 46, 73), and the male was 58.3%. Among 446 patients, 181 (40.6%) came from the emergency department, and 127 (28.5%) came from the general wards. Median APACHE II and SOFA scores were 23 points (IQR 18, 30) and 8 (IQR 5, 11), respectively. The median Charlson comorbidities index

Table 1. Baseline characteristics of intensive care unit patients by mortality at day 28

Characteristic	All patients (446)	Survivors (309)	Non-survivors (137)	p-value
Age, median (IQR), years	60 (46, 73)	60 (47, 74)	59 (41, 72)	0.40
Male sex, No. (%)	260 (58.3)	186 (60.2)	74 (54.0)	0.26
Body mass index, median (IQR), kg/m^2	21.5 (18.7, 24.2)	21.8 (18.7, 24.2)	21.4 (18.5, 24.1)	0.54
SOFA, median (IQR), points	8 (5, 11)	6 (4, 9)	11 (9, 16)	<0.001*
APACHE II, median (IQR), points	23 (18, 30)	21 (16, 27)	29 (23, 37)	<0.001*
Charlson comorbidities index, median (IQR), points	4 (2,6)	4 (2, 6)	5 (3, 7)	0.022*
Comorbidities, No. (%)				
DM	149 (33.4)	112 (36.2)	37 (27.0)	0.07
CKD stage 3 to 5	123 (27.6)	83 (26.9)	40 (29.2)	0.69
CVS diseases	90 (20.2)	62 (20.1)	28 (20.4)	0.99
Malignancies	60 (13.5)	34 (11.0)	26 (19.0)	0.03*
Neurologic diseases	57 (12.8)	45 (14.6)	12 (8.8)	0.12
Connective tissue diseases	55 (12.3)	32 (10.4)	23 (16.8)	0.08
Cirrhosis	48 (10.8)	22 (7.1)	26 (19.0)	<0.001*
Chronic pulmonary disease	35 (7.8)	23 (7.4)	12 (8.8)	0.78
AIDS	16 (3.6)	10 (3.2)	6 (4.4)	0.58
ICU admission source, No. (%)				
Emergency department	181 (40.6)	140 (45.3)	41 (29.9)	<0.001*
Ward	127 (28.5)	85 (27.5)	42 (30.7)	
HDU or intermediate care	39 (8.7)	16 (5.2)	23 (16.8)	
Other ICU	13 (2.9)	8 (2.6)	5 (3.6)	
Other hospital	86 (19.3)	60 (19.4)	26 (19.0)	
Reason for ICU admission, No. (%)				
Acute respiratory failure	265 (59.4)	162 (52.4)	103 (75.2)	<0.001*
Sepsis/septic shock	175 (39.2)	96 (31.1)	79 (57.7)	<0.001*
Shock (exclude septic shock)	64 (14.3)	38 (12.3)	26 (19.0)	0.087
AKI requiring RRT	72 (16.1)	33 (10.7)	39 (28.5)	<0.001*
Neurologic conditions	41 (9.2)	24 (7.8)	17 (12.4)	0.17
Acute abdomen	10 (2.2)	9 (2.9)	1 (0.7)	0.30
Acute coronary syndrome	6 (1.3)	6 (1.9)	0 (0.0)	0.18
Post-operation	9 (2.0)	8 (2.6)	1 (0.7)	0.29
Other	53 (11.9)	47 (15.2)	6 (4.4)	0.002*

AIDS=acquired immunodeficiency syndrome; AKI=acute kidney injury; APACHE=acute physiology, age, chronic health evaluation; CKD=chronic kidney disease; CVS=cardiovascular disease; DM=diabetes mellitus; HDU=high dependence unit; ICU=intensive care unit; IQR=interquartile range; RRT=renal replacement therapy; SOFA=sequential organ failure assessment

*$p<0.05$ when compared with survivors

was 4 points (IQR 2, 4). In addition, the authors found that diabetes mellitus was the most common comorbid (33.4%), followed by chronic kidney disease stage 3 to 5 (27.6%). For the principal diagnosis of hospital admission by ICD 10, infectious diseases (A00 to B99) and respiratory diseases (J00 to J99) were the main diagnosis, 20.9% and 20.4%, respectively. However, the most common reason for ICU admission was ARF (59.4%), followed by sepsis/septic shock (39.2%) (Table 1).

Acute respiratory failure and support

Of the 446 patients, 308 (69.1%, 95% CI 61.7 to 70.2) developed ARF. Of those, 252 patients (81.1%) received invasive mechanical ventilation before ICU admission, while 56 patients (18.2%) received it after. For respiratory support, 313 (70.2%) received invasive mechanical ventilation, and 30 (6.8%) received non-invasive ventilation. Median duration of mechanical ventilation was 6 days (IQR 2, 15; 95% CI 4 to 6), whereas the ventilator-free day on day 28 was 22 days (IQR 0, 28; 95% CI 16 to 23). Of 313 invasively ventilated patients, 34 patients (10.9%) were reintubated. The median time to the first reintubation was 2 days (IQR 1, 3).

Forty-one (13.1%, 95% CI 9.8 to 17.3) patients developed ventilator-associated events. The incidence rate of VAE was 14.8 events per 1,000 ventilator-days (95% CI 10.6 to 20.1). The authors found VAC 14 patients (4.5%), IVAC 1 patients (0.3%), possible VAP 26 patients (8.3%) (Table 2). The incidence rate of possible VAP was 9.4 events per 1,000 ventilator-days (95% CI 6.1 to 13.8).

Table 2. Respiratory failure and support in intensive care unit patients by mortality at day 28

Characteristic	All patients (446)	Survivors (309)	Non-survivors (137)	p-value
Acute respiratory failure, No. (%)	308/446 (69.1)	182/309 (58.9)	126/137 (92.0)	<0.001*
Before ICU admission	252/308 (81.8)	156/182 (85.7)	96/126 (76.2)	0.048*
After ICU admission	56/308 (18.2)	26/182 (14.3)	30/126 (23.8)	
Mechanical ventilation, No. (%)	313 (70.2)	186 (60.2)	127 (92.7)	<0.001*
Non-invasive ventilation, No. (%)	30 (6.8)	26 (8.5)	4 (2.9)	0.052
Duration of mechanical ventilation, median (IQR), days	6.0 (2.0,15.0)	5.5 (3.0,14.8)	6.0 (1.5,15.0)	0.46
VFD at day 28, median (IQR), days	22 (0.0, 28.0)	26 (19.0, 28.0)	0.0 (0.0, 0.0)	<0.001*
Ventilator associated events, No. (%)				
No ventilator associated events	272/313 (86.9)	173/186 (93.0)	99/127 (78.0)	<0.001*
VAC	14/313 (4.5)	5/186 (2.7)	9/127 (7.1)	
Infection related VAC	1/313 (0.3)	1/186 (0.5)	0/127 (0.0)	
Possible VAP	26/313 (8.3)	7/186 (3.8)	19/127 (15.0)	

ICU=intensive care unit; IQR=interquartile range; VFD=ventilator free day; VAC=ventilator associated complication; VAP=ventilator associated pneumonia

*p<0.05 when compared with survivors

Table 3. Acute kidney injury and renal support in intensive care unit patients by mortality at day 28

Characteristic	All patients (446)	Survivors (309)	Non-survivors (137)	p-value
Acute kidney injury, No. (%)	278/389 (71.5)	163/265 (61.5)	115/124 (92.7)	<0.001*
Stage I AKI	70/278 (25.2)	62/163 (38.0)	8/115 (7.0)	<0.001*
Stage II AKI	57/278 (20.5)	39/163 (23.9)	18/115 (15.7)	
Stage III AKI	151/278 (54.3)	62/163 (38.0)	89/115 (77.4)	
Renal replacement therapy, No. (%)				
CRRT	91/278 (32.7)	32/163 (19.6)	59/115 (51.3)	<0.001*
HD	28/278 (10.1)	20/163 (12.3)	8/115 (7)	0.21
PD	1/278 (0.4)	1/163 (0.6)	0/115 (0.0)	0.99
Duration of RRT, median (IQR), days				
CRRT duration	3 (2.0, 4.0)	3.0 (2.0, 4.25)	3.0 (2.0, 4)	0.99
HD sessions	2 (1, 3)	2 (1, 3.5)	2 (1.75, 2.25)	0.18
PD duration	11 (11, 11)	11 (11, 11)	NA	NA
Cumulative fluid balance, median (IQR), mL	3,71.8 (319, 8,031)	1,855 (-475, 5,740)	8,755 (4,639, 15,661)	<0.001*
Fluid overload, median (IQR), %	2.2 (0.3, 6.6)	1.5 (-0.1, 4.5)	3.5 (1.5, 11.4)	<0.001*

AKI=acute kidney injury; CRRT=continuous renal replacement therapy; IQR=interquartile range; HD=hemodialysis; PD=peritoneal dialysis; RRT=renal replacement therapy.

*p<0.05 when compared with survivors

Acute kidney injury and support

Fifty-seven patients presented with a history of end-stage kidney disease. Hence, 389 patients were at risk of AKI. Of 389 patients, 278 patients (71.5%, 95% CI 66.8 to 75.7) developed AKI: 70 patients (25.2%) developed stage I AKI, 57 patients (20.5%) developed stage II AKI, and 151 patients (54.3%) develop stage III AKI. The median CRRT duration among AKI patients was 3 days (IQR 2,4), and the median hemodialysis session was 2 sessions (IQR 1,3). Only one AKI patient received peritoneal dialysis for 11 days. After ICU discharge, patients had positive fluid balance with a median amount of 3,718 mL (IQR 319, 8031) and fluid overload of 2.2% (IQR 0.3, 6.6) (Table 3).

Shock and hemodynamic support

Shock developed in 298 patients (66.8%, 95% CI 62.3 to 71.0). Septic shock was the most frequent at about 75.5%, followed by hypovolemic shock at 47%, cardiogenic shock at 11.1%, and obstructive shock at 3%.

Norepinephrine was the most common vasoactive medication used in shock patients at about 79.5% of the patients with a median dosage of 0.2 µg/kg/min (IQR 0.09, 0.39) and range between 0.02 to 3 µg/kg/min. Epinephrine was dispensed at about 28.2% with a median dosage of 0.87 µg/kg/min (IQR 0.37, 2.08) and a range between 0.1 to 5 µg/kg/min. Dopamine and dobutamine were prescribed at about 15.1 and 5%, respectively (Table 4).

Nutrition support

377 patients (84.5%, 95% CI 80.9 to 87.6) received either enteral or parenteral nutrition. The median time from ICU admission to start nutrition support was 1 day (IQR 1.0, 2.0). Enteral nutrition was started in 98.4%, whereas parenteral nutrition was administered at about 4.5%.

Hospital and intensive care unit outcomes

The authors considered death status in terminal illness patients discharged from the hospital to home with end-of-life care. Among 446 patients, 121 (27.1%, 95% CI 23.2 to 31.4) died in ICU, and 167 (37.4%, 95% CI 33.1 to 42.0) died in the hospital. Mortality at day 28, day 90, and 1 year were 30.7% (95% CI 26.6 to 35.1), 42.4% (95% CI 37.9 to 47), and 53.8% (95% CI 49.2 to 58.4), respectively. Mortality at day 28 increased according to the severity of

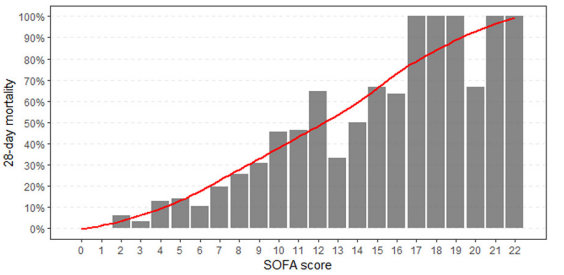

Figure 1. Bar graph and line plot of 28-day mortality by SOFA score.

Table 4. Shock and hemodynamic support in intensive care unit patients by mortality at day 28

Characteristic	All patients (446)	Survivors (309)	Non-survivors (137)	p-value
Shock, No. (%)	298/446 (66.8)	175/309 (56.6)	123/137 (89.8)	<0.001
Hypovolemic shock	140/298 (47.0)	94/175 (53.7)	46/123 (37.4)	0.008
Septic shock	225/298 (75.5)	114/175 (65.1)	111/123 (90.2)	<0.001
Cardiogenic shock	33/298 (11.1)	20/175 (11.4)	13/123 (10.6)	0.96
Obstructive shock	9/298 (3.0)	4/175 (2.3)	5/123 (4.1)	0.50
Adrenal shock	4/298 (1.3)	4/175 (2.3)	0/123 (0.0)	0.15
Vasopressors/Inotropes, No. (%)				
Norepinephrine	237/298 (79.5)	117/175 (66.9)	120/123 (97.6)	<0.001
Dose, median (IQR), µg/kg/min	0.20 (0.09, 0.39)	0.11 (0.06, 0.17)	0.36 (0.23, 0.63)	<0.001
Dose, range, µg/kg/min	0.02 to 3.00	0.02 to 0.56	0.02 to 3.00	
Epinephrine	84/298 (28.2)	11/175 (6.3)	73/123 (59.3)	<0.001
Dose, median (IQR), µg/kg/min	0.87 (0.37, 2.08)	0.30 (0.18, 0.41)	1.06 (0.42, 2.22)	<0.001
Dose, range, µg/kg/min	0.10 to 5.00	0.10 to 0.98	0.13 to 5.00	
Dopamine	45/298 (15.1)	15/175 (8.6)	30/123 (24.4)	<0.001
Dose, median (IQR), µg/kg/min	13.30 (6.04, 16.60)	6.50 (2.87, 13.70)	15.55 (9.95, 19.23)	0.015
Dose, range, µg/kg/min	1.15 to 33.30	1.15 to 21.80	1.90 to 33.30	
Dobutamine	15/298 (5.0)	8/175 (4.6)	7/123 (5.7)	0.87
Dose, median (IQR), µg/kg/min	4.00 (2.42, 5.12)	3.03 (2.31, 3.92)	5.20 (4.20, 6.00)	0.029
Dose, range, µg/kg/min	2.08 to 6.94	2.08 to 5.05	2.38 to 6.94	

IQR=interquartile range

*p<0.05 when compared with survivors

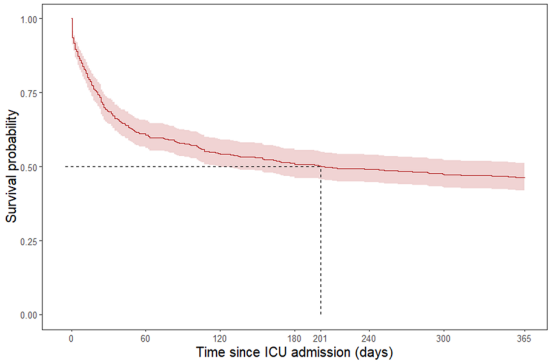

Figure 2. One-year Survival probability after ICU admission. The dashed line is the median survival time.

organ failure as assessed by SOFA score (Figure 1). The median ICU length of stay was 5 days (IQR 3, 12, 95% CI 5 to 6) and the median hospital length of stay was 15 days (IQR 7, 31, 95% CI 11.5 to 16). Median survival time was 201 days (95% CI 120 to -) (Figure 2).

Factors associated with mortality

Patients who expired within 28 days had a significantly higher comorbidity index, the severity of illness, and positive fluid balance. Non-survived patients also had a greater prevalence of ARF with or without ventilator-associated events, AKI, especially from stage II and stage III AKI, and shock mainly from septic shock and obstructive shock (Table 5).

Table 5. Factors associated with non-survivor patients at day 28 on univariable Cox proportional hazards model

Variable	Univariable analysis*		
	HR	95% confidence interval	p-value
Age, years*	1.00	1.00 to 1.01	0.19
Male	0.94	0.73 to 1.21	0.62
Body mass index, kg/m^{2}*	0.98	0.95 to 1.01	0.29
SOFA, points*	1.19	1.16 to 1.23	<0.001
APACHE II, points*	1.10	1.08 to 1.12	<0.001
Charlson comorbidities index, points*	1.09	1.05 to 1.14	<0.001
ICU admission source			
Emergency department	1.00	Ref	Ref
Ward	1.62	1.18 to 2.22	0.003
HDU or intermediate care	2.97	1.96 to 4.49	<0.001
Other ICU	1.28	0.56 to 2.94	0.56
Other hospital	1.36	0.94 to 1.96	0.10
Acute respiratory failure	2.72	1.96 to 3.77	<0.001
Ventilator associated events			
No VAE	1.00	Ref	Ref
VAC	2.63	1.47 to 4.72	<0.001
VAP	2.57	1.68 to 3.94	<0.001
Acute kidney injury			
No AKI	1.00	Ref	Ref
Stage I AKI	1.14	0.74 to 1.75	0.55
Stage II AKI	1.59	1.03 to 2.46	0.036
Stage III AKI	3.36	2.47 to 4.57	<0.001
Cumulative fluid, Liter*	1.07	1.06 to 1.09	<0.001
Fluid overload, %*	1.03	1.02 to 1.04	<0.001
Shock	2.68	1.95 to 3.66	<0.001
Hypovolemic shock	1.15	0.88 to 1.50	0.31
Septic shock	2.68	2.05 to 3.50	<0.001
Cardiogenic shock	1.38	0.88 to 2.16	0.16
Obstructive shock	2.35	1.16 to 4.75	0.018
Adrenal shock	0.72	0.18 to 2.88	0.64
Nutritional support	0.19	0.14 to 0.26	<0.001

AKI=acute kidney injury; APACHE=acute physiology, age, chronic health evaluation; HDU=high dependence unit; HR=hazard ratio; ICU=intensive care unit; SOFA=sequential organ failure assessment; VAC=ventilator associated complication; VAE=ventilator associated event; VAP=ventilator associated pneumonia

*per 1-point increase

The authors performed a multivariable Cox proportional hazards model to evaluate the effect of organ failure on mortality; however, the proportional hazard assumption was violated, the respective variables were introduced into the model as a time-varying covariate using natural cubic splines, resulting in nonconstant HR over the follow-up time. The final model included age, Charlson comorbidity index, shock, ARF, AKI as predictors. ARF constantly affected from time to death at day 28 (HR 3.68, 95% CI 1.96 to 6.91, p<0.001). However, shock and AKI had time-varying effects. The shock had a peak effect on mortality since day 1 of ICU admission (HR 120.3, 95% CI 4.76 to 3,040.7) and this effect decreased exponentially but still had a significant impact on day 28 (HR 2.07, 95% CI 1.14 to 3.74) (Figure 3). Development of stage III AKI significantly affected mortality since day 3.17 of ICU admission (HR 2.26, 95% CI 1.01 to 4.30). However, the development of stage II AKI had a significant effect at day 21.68 (HR 1.93, 95% CI 1.002 to 3.75). Both stage II and stage III AKI had a peak effect on day 28. The development of stage I AKI did not affect to 28-day survival of patients (Figure 4). Patients with shock had the lowest predicted survival probability, followed by ARF and AKI (Figure 5).

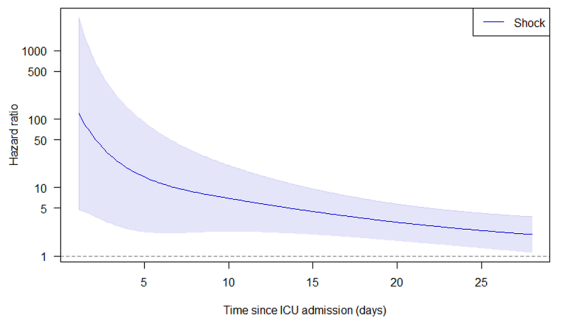

Figure 3. Time-dependent hazard ratio (solid line) wtih 95% confidence interval (shaded area) of shock for 28-day mortality.

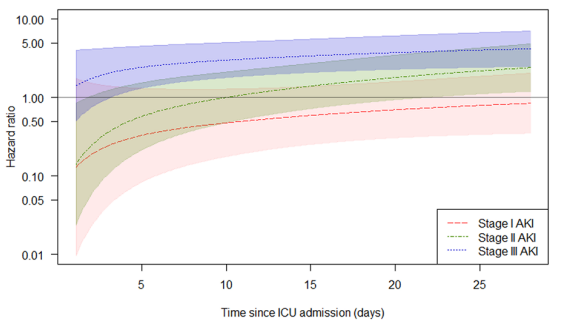

Figure 4. Time-dependent hazard ratio (solid line) wtih 95% confidence interval (shaded area) of acute kidney injury for 28-day mortality.

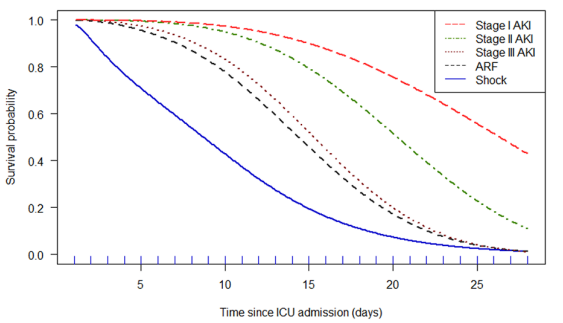

Figure 5. Predicted survival probabality at day 28 by organ failure.

Discussion

General characteristics of our ICU regarding severity scores upon the first 24 hours of ICU admission were relatively higher compared to other Asia countries and European countries[1,23,24]. The mean APACHE II and SOFA scores of South East Asia ICU were 16.9 and 6.4, respectively[24,25]. This difference came from our hospital, which is the university referral hospital. Thailand is categorized as an upper-middle-income country; however, high-income countries had a higher severity score than upper-middle-income, lower-middle-income, and low-income countries[26].

Our study found that AKI is the most common organ failure at some point during ICU stay, followed by ARF and shock. The multicenter study of organ failure in the United Kingdom[27] using SOFA scored 3 to 4 points as a failure definition, demonstrating that ARF was the most common organ failure. Using the KDIGO definition for AKI is more sensitive to detecting the early stage of AKI than the SOFA score.

Most of the patients with ARF developed before ICU admission, which was the main reason for ICU admission. Non-invasive ventilation utilization was lower compared to other studies[28] because the availability of NIV outside the ICU, including the emergency department, is low. Prevalence of VAE and subcategories of VAE in the present study was lower than pool prevalence of meta-analysis[29]. VAE definition is objective, reproducible and automation using electronic medical record. Recent guideline for VAP surveillance recommend using CDC's VAE definition[30].

The two-thirds and a half of ICU patients had shock and septic shock at any time point, respectively, while the SOAP study showed one-third had shock and septic shock in China and Turkey were around 25% of ICU patients[31,32]. Because our hospital is a referral hospital and studying in medical ICU, the prevalence of septic shock was high. Norepinephrine was the most common catecholamine used that was in line with the previous studies[33]. The median dose of norepinephrine in our study was lower than the SOAP study both in survivors (0.11 vs. 0.5 µg/kg/min) and

non-survivors (0.36 vs. 0.7 µg/kg/min). The median dose of epinephrine is lower in survivors (0.3 vs. 0.6 µg/kg/min) but higher in non-survivors (1.06 vs. 0.8 µg/kg/min) compared with the SOAP study[33]. Because vasopressin is unavailable in Thailand, the authors use epinephrine as a second vasopressor. However, the appropriate timing to start epinephrine is controversial. A longer duration of epinephrine administration was associated with poor outcomes[34].

Hospital mortality (37%) was higher than ICU mortality (27%) at about 10% in the present study. The difference reflects ICU discharge practices such as discharge criteria, bed allocation, early discharge planning, and step-down facilities[35]. Short-term mortality and one-year mortality were higher compared to developed countries that corresponded with higher severity of illness. Patients with shock had the lowest survival probability, followed by patients with ARF and AKI. The authors found that shock was far more strongly associated with mortality.

Similar to the study from TK Nfor, et al.[6], the odds of death is highest in cardiovascular SOFA failure. Likewise, the study from Bingold TM, et al.[36] found that cardiovascular failure had the highest impact on mortality, followed by liver failure, respiratory failure, renal failure, and coagulation failure, respectively. Moreover, the authors found that the effect of shock on mortality contributed up to 28 days.

The present study has several limitations. First, the study was a single-center study in a university hospital. The population of patients might not represent general critically ill patients. Second, there is a lack of detail on each organ failure, such as the severity of ARF, ventilatory parameters, shock time, shock reversal time, and calorie intake. Third, the study was conducted only in medical ICU. However, the authors had no missing data and collected data in consecutive all patients that can reflect a big picture of critically ill medical patients. In addition, the authors explore the time-varying effect of individual organ failure, leading to a weighting score of organ failure to predict mortality in a specific time. Finally, our suggestions are about prioritization of organ rescue in multiorgan failure patients. For instance, the authors might have conservative fluid management to shorten ventilator time, although it might develop acute kidney injury. Future studies are about organ support interactions and the importance of other organ failures, such as hematologic, neurologic, and liver failure.

Conclusion

Medical intensive care units had a high severity of illness. AKI and ARF frequently developed in critically ill medical patients. Individual organ failure contributed to mortality in different fashions. Shock was a high impact on mortality. In-hospital mortality and long-term mortality were still high after ICU discharge.

What is already known on this topic?

Organ failures are common in ICU. Medical ICU have a higher severity of illness than other types of ICU. ARF and shock are the most common reasons to admit in medical ICU.

What this study adds?

Critically ill medical patients in Thailand were high severity of illness and mortality. Therefore, the data can provide a benchmark for other ICU in Thailand to improve the quality of care. Because of the high post-ICU mortality, the authors have room for improvement in post-ICU discharge care and discharge criteria. In addition, shock produces mortality more than other types of organ failure.

Acknowledgements

This study received funding from the Faculty of Medicine, Khon Kaen University (IN58245). The authors thank the Department of Medicine, Faculty of Medicine, Khon Kaen University for publication support.

Conflict of interest

The authors declare no conflict of interest.

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