Factors Associated with Mortality of Intensive Care Unit Patients with Acute Kidney Injury at Cipto Mangunkusumo National Central General Hospital

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ABSTRAK

Latar belakang: *kejadian acute kidney injury (AKI) di unit perawatan intensif berhubungan dengan peningkatan mortalitas, morbiditas pasca AKI dan biaya perawatan tinggi. Penelitian mengenai faktor-faktor yang berhubungan dengan mortalitas pasien AKI di unit perawatan intensif di Indonesia khususnya RSUPN dr. Cipto Mangungkusumo belum pernah dilakukan. Penelitian ini bertujuan untuk mengetahui prevalensi AKI, angka mortalitas pasien AKI, dan faktor- faktor yang berhubungan dengan peningkatan mortalitas pasien AKI di unit perawatan intensif di ICU RSUPN dr. Cipto Mangunkusumo.* ***Metode:*** *penelitian kohort retrospektif terhadap seluruh pasien AKI di unit perawatan intensif di RSUPN Cipto Mangunkusumo periode Januari 2015 – Desember 2016. Dilakukan analisis hubungan bivariat sampai dengan multvariat dengan STATA Statistics 15.0 antara faktor usia >60 tahun, sepsis, ventilator, durasi ventilator, dialisis, oligoanuria, dan skor APACHE II saat admisi dengan mortalitas.* ***Hasil:*** *prevalensi pasien AKI di unit perawatan intensif didapatkan 12,25% (675 dari 5511 subjek) dan sebanyak 220 subjek (32,59%) dari 675 subjek yang dianalisis meninggal di unit perawatan intensif. Faktor-faktor yang berhubungan dengan peningkatan mortalitas pada analisis multivariat adalah sepsis (OR 6,174; IK95% 3,116-12,233), oligoanuria (OR 4,173; IK95% 2,104-8,274), ventilator (OR 3,085; IK95% 1,348-7,057), (skor APACHE II saat admisi)1/2 [OR 1,597; IK95% 1,154-2,209], dan durasi ventilator (OR 1,062; IK95% 1,012-1,114).* ***Kesimpulan:*** *prevalensi pasien AKI dan angka mortalitasnya di unit perawatan intensif RSUPN dr. Cipto Mangunkusumo didapatkan sebesar 12,25% dan 32,59%. Sepsis, oligoanuria, ventilator, (skor APACHE II saat admisi)1/2, dan durasi ventilator merupakan faktor-faktor yang berhubungan bermakna dengan peningkatan mortalitas pasien AKI di unit perawatan intensif.*

Kata kunci: *acute kidney injury, faktor risiko, mortalitas, unit perawatan intensif.*

ABSTRACT

Background: *the incidence of acute kidney injury (AKI) in intensive care units is associated with increased mortality, post AKI morbidity and high treatment costs. Research on factors related to mortality of AKI patients in intensive care units in Indonesia, especially Cipto Mangungkusumo General Hospital has never been done. This study aims to determine the prevalence of AKI, mortality rate of AKI patients, and the factors associated with increased*

mortality of AKI patients in intensive care units in ICU Cipto Mangunkusumo General Hospital. ***Methods:*** *this is a retrospective cohort study of all patients diagnosed with AKI in the intensive care unit at Cipto Mangunkusumo General Hospital, January 2015 - December 2016. An analysis of bivariate relationships with multvariate with STATA Statistics 15.0 between age > 60 years, sepsis, use of ventilator, ventilator duration, dialysis, oligoanuria, and APACHE II scores at admission with mortality.* ***Results:*** *the prevalence of AKI patients in the intensive care unit was 12.25% (675 of 5511 subjects) and 220 subjects (32.59%) of the 675 analyzed subjects died in the intensive care unit. Factors related to increased mortality in multivariate analysis were sepsis (OR 6,174; IK95% 3,116-12,233), oligoanuria (OR 4,173; IK95% 2,104-8,274), use of ventilator (OR 3,085; IK95% 1,348-7,057), (scores APACHE II at admission) 1/2 [OR 1,597; IK95% 1.154-2.209], and the duration of the ventilator (OR 1.062; IK95% 1.012-1.114).* ***Conclusion:*** *the prevalence of AKI patients and their mortality rate in the intensive care unit of Cipto Mangunkusumo General Hospital obtained 12.25% and 32.59%. Sepsis, oligoanuria, ventilators (APACHE II score at admission) 1/2, and ventilator duration are factors that are significantly associated with increased mortality of AKI patients in intensive care units.*

Keywords: *acute kidney injury, risk factors, intensive care unit, mortality.*

INTRODUCTION

Acute kidney injury (AKI) is currently a major health problem worldwide with AKI incidence ranges from 20 to 200 cases per 1 million population in community and 5.4 to 288 cases per 100,000 population in hospital with a mortality rate of 1.7 million deaths per year.[1] The majority of AKI cases occur in ICU patients with incidence ranges from 15.8 to 65% and high mortality rates is also found ranging from 24 to 64.7%.[2–8] Post-AKI outcomes include increased risk of chronic kidney disease and end-stage renal disease, longer duration of hospitalization, higher mortality at both hospital and post-hospital care, as well as high costs of AKI care reaching USD$ 1,700,000 per year in the United States.[9–11]

Several studies have been conducted to identify factors related to mortality of ICU patients with AKI. These factors include metabolic acidosis, use of mechanical ventilation, APACHE II score, advance AKI stage, hypotension, higher creatinine levels, leukocytosis, hyperkalemia and blood urea level at the time of diagnosis of AKI are the predictors of in-hospital mortality of ICU patients with AKI.[6,8] But these risk factors may differ between countries, probably because of the difference patient characteristics (race, age, cause of AKI) and healthcare system where the study was conducted. To date, there is no study assessing risk factors of mortality in ICU patients in AKI. Based on the above mentioned consideration, it is necessary to conduct a study on factors associated with mortality of ICU patients with AKI. To date, no study has been conducted in Indonesia addressing the issue.

METHODS

A retrospective cohort study was conducted among adults (>18 years old) critically ill patients with who were treated at Cipto Mangunkusumo Hospital (RSCM), Jakarta, a tertiary national level referral hospital in Indonesia during January 2015 to December 2016 period. Patients who had been previously diagnosed with Chronic Kidney Disease (CKD), had received routine dialysis prior to the study, had a kidney transplant and those who had been diagnosed with AKI, but subsequently died within <48 hours during their hospitalization in the ICU were excluded. Demographic, clinical and laboratory data were obtained from medical records and electronic health record (EHR). The diagnosis of AKI was reestablished by the authors using KDIGO classification. The protocol of the study been approved by the Research Ethics Committee, Faculty of Medicine, Universitas Indonesia/Cipto Mangunkusumo Hospital, reference number 434/UN2.F1/ETIK/2017 on May 8th, 2017.

The primary outcome was mortality rate of ICU patients with AKI who were hospitalized more than 48 hours. Subjects will be classified as survivor and non-survivor AKI. There were seven variables that had been assessed including patients with the age of > 60 years old, patients

with sepsis, patients with mechanical ventilator, duration of ventilator use, dialysis, oligoanuria, and score of Acute Physiology and Health Chronic Evaluation (APACHE) II at admission. Sepsis was assessed based on the following criteria i.e. the presence of clear or suspected focus of infection and an acute increase in SOFA score of ≥ 2.12 Urine production of <400 ml / 24 hours was considered as oligouria and urine production of <50 ml / 24 hours was considered as anuria.[13]

Data were analyzed using STATA Statistics software program version 15.0. Bivariate analysis was utilized to observe the correlation between dependent and independent variables using Chi square statistical test for categorical variables, unpaired t-test for APACHE II score variable at admission, and Mann Whitney test for ventilator duration variable. Subsequently, the analyses of those variables were continued into a multivariate model when the bivariate analysis showed p value of <0.25. Statistically significant was considered when $p < 0.05$.

RESULTS

There were 5511 subjects aged ≥18 years who were admitted to the ICU between January 2015 and December 2016. About 1349 out of 5511 subjects who were diagnosed with AKI based on medical records, 674 subjects had met the exclusion criteria (CKD, previous history of renal transplantation, routine dialysis and death occurred within 48 hours after ICU admission); therefore, only 675 subjects were included in our study. The median age in this study was 49 years old and the majority of subjects were male (63.41%); while the prevalence of AKI in ICU patients was 12.25% (675 out of 5511). The diagnosis of AKI was reestablished by the author and we found a discrepancy of AKI diagnosis in 199 subjects out of 675 subjects (29.48%).

The proportions of AKI events based on the sites of study were 36.44% for Emergency Room/ ER ICU, 20.77% for ICU Center, 13.63% for Burn Unit ICU, 13.04% High Care Unit, 11.26% for Intensive Coronary Care Unit/ICCU, 3.56% for Cardiac Intensive Care Unit/CICU and 1.33% for the other HCU. Most patients (90.81%) had National Health Insurance as their financial support. Based on the onset, AKI was commonly found in most of ICUs except in ICCU and ER ICCU, where most of AKI had occurred before the patients were admitted to the ICU (65.79% and 53.25%).

The majority of the subjects with AKI in our study had received nephrotoxic drugs (97.93%) and mostly had taken Proton Pump Inhibitors/ PPI (68.89%), carbapenem (49.04%), and cephalosporin (40.89%). The mortality rate of patients with AKI in the ICU was 32.59% (220 of 675 subjects) with the top three leading cause of death were sepsis shock (88.64%), respiratory failure (5.45%) and cardiovascular complications (4.09%). The baseline subject characteristics are shown in **Table 1**.

Bivariate and Multivariate Analyses on Risk Factors Associated with Mortality

Death was occurred in 220 out of 675 (32.59; 95% CI 32.56 – 32.63). In bivariate analysis, there were six variables associated mortality in ICU patients with AKI i.e. sepsis, mechanical ventilator, duration of ventilator use, dialysis, oligoanuria, and APACHE II score at admission. The variables with $p < 0.25$ found in the bivariate analysis were subsequently included in the multivariate analysis. In multivariate analysis using logistic regression, we found five variables with p <0.05 as shown in **Table 2**.

DISCUSSION

The mortality rate of ICU patients with AKI in our study was 32.59%. The rate is lower than the result found in a study, which was conducted by Andrikos et al.[3] and Wijewikamaama et al8; but it is similar to the result in a study conducted by Ralib et al[14]. Our results have similar characteristics with results demonstrated by Ralib et al.[14] i.e. the AKI criteria were based on KDIGO criteria, the subjects were those who were ≥18 years old, were hospitalized in the ICU with a duration of ≥48 hours, most patients were male at the same age with a median age of 50 years and sepsis was observed in 2/3 of patients with AKI.

Factors Associated With Mortality

In our study, we found that the proportion of patients aged > 60 years in the survivor AKI group and the non-survivor AKI group was not

Table 1. Basic subject characteristics

Variables	Total AKI (n=675)	Survivor AKI (n=455)	Non-Survivor AKI (n=220)
Male [n(%)]	428 (63.41)	291 (63.96)	137 (62.27)
Age (y.o) [median (min-max)]	49 (18-90)	49 (18-90)	50 (18-86)
Age >60 y.o [n (%)]	147 (21.78)	97 (21.32)	50 (22.73)
Length of stay (days) [median (min-max)]	7 (1-78)	6 (1-65)	9 (1-78)
AKI onset [(n)%]			
- Pre-ICU	323 (47.85)	232 (50.99)	91 (41.36)
- In ICU	332(52.15)	223 (49.01)	129 (58.64)
AKI severity [n (%)]			
- AKI I	487 (72.15)	357 (78.46)	130 (59.64)
- AKI II	66 (9.78)	37 (8.13)	29 (13.18)
- AKI III	122 (18.07)	61 (13.41)	61 (27.73)
Sepsis [(n)%]	411 (60.89)	208 (45.71)	203 (92.27)
Dialysis [(n)%]	74(10.96)	27 (5.93)	47 (21.36)
- Intermittent hemodialysis	39 (5.78)	21 (4.62)	18 (8.18)
- CRRT	27 (4.0)	4 (0.88)	23 (10.45)
- Combination	8 (1.19)	2 (0.44)	6 (2.73)
Ventilator Mechanic [n (%)]	454 (67.26)	252 (55.38)	202 (91.82)
Duration of ventilator use (days) [median (min-max)]	2 (0-49)	1 (0-47)	7 (0-49)
Oligoanuria (n=414) [(n)%]	66 (15.94)	25 (8.50)	41 (34.17)
Urine Output (cc/kgBW/day) [median (min-max)]	0.985 (0-4.75)	1.01 (0-4.75)	0.73 (0-3.9)
APACHE II score at ICU admission (n=441) [median (min-max)]	8 (0-30)	7 (0-30)	11 (2-25)
Contrast agents [n(%)]	110 (16.30)	94 (20.66)	16 (7.27)
Surgery [n(%)]	418 (61.93)	288 (63.30)	130 (59.09)
Nephrotoxic drugs [n(%)]	661(97.93)	444 (97.58)	217 (98.64)
Vasopressors [n(%)]	377 (55.85)	175 (38.46)	202 (91.82)
Comorbidities [n(%)]			
- Diabetes Mellitus	99 (14.67)	72 (15.82)	27 (12.27)
- Cardiovascular[a]	244 (36.15)	182 (40)	62 (28.18)
- Cerebrovascular[b]	59 (8.74)	43 (9.45)	16 (7.27)
- Pulmonary[c]	276 (40.18)	158 (34.73)	118 (53.64)
- Malignancy	116 (17.19)	82 (18.02)	34 (15.45)
- Others[d]	49 ((7.25)	37 (8.13)	12 (5.45)
Creatinine level (mg/dL) [median (min-max)]	1.45 (0.47-12.4)	1.4 (0.5-9.59)	1.7 (0.47-12.4)
Plasma pH [median (min-max)]	7.39 (6.96-7.67)	7.403 (7.0-7.673)	7.371 (6.96-7.66)
Bicarbonate level (mEq/L) [median (min-max)]	21 (5-47.5)	21.2 (4.0-47.5)	20.6 (7.8–42.9)
Pottasium (mEq/L) [median (min-max)]	4.13 (2.1-7.87)	4.1 (2.1 – 7.6)	4.35 (2.3-7.87)

AKI, Acute Kidney Injury; APACHE, Acute Physiology and Chronic Health Evaluation; CRRT, Continuous Renal Replacement Therapy. a Including hypertension, coronary arterial disease and chronic heart failure b Including stroke, trauma, dissecting aneurysm, and infection, c Including pneumonia, chronic obstructive pulmonary disease, and pulmonary tuberculosis. dIncluding chronic liver disease, hepatitis B and C, cirrhosis hepatis, autoimmune, dan Acquired Immunodeficiency Syndrome (AIDS).

different. Studies by Bucuvic et al[15] and Elhendy et al.[16] have suggested that the age of > 60 years is a factor associated with a 3-folds higher mortality risk in subjects with AKI. The higher mortality risk is associated with renal epithelial cell proliferation disorder and progenitor cell as well as stem cell function due to aging process.[15] In contrast to the results of those studies, our

Table 2. Bivariate and multivariate analysis

Variables	Bivariate Analysis		Multivariate Analysis	
	RR (95%CI)	P	OR (95%CI)	P
Sepsis	7.67 (4.793-12.274)	< 0.001	6.174 (3.116-12.233)	< 0.001
Ventilator Mechanic	5.463 (3.468-8.606)	< 0.001	3.085 (1.348-7.057)	< 0.001
Duration of Ventilator use	-	<0.001*	1.062 (1.012-1.114)	0.015
Oligoanuria	2.736 (2.088-3.586)	< 0.001	4.173 (2.104-8.274)	< 0.001
(APACHE II score at admission)1/2**	(-0.819- (-0.466))	< 0.001***	1.597 (1.154—2.209)	0.005
Dialysis	2.206 (1.782-2.732)	< 0.001	1.034 (0.419-2.555)	0.942

APACHE, Acute Physiology and Chronic Health Evaluation. * Mann Whitney test. ** Normalization with squareroot.
** Unpaired t-test

study showed that the age of > 60 years was not associated with higher mortality among ICU patients with AKI. It may occur since the median age found in our study was 49 years old and the proportion of patients aged > 60 years was 21.78%. Our findings support the result of a study by Lameire et al.[17], which found that older age is not associated with higher mortality rate among patients with AKI.

The proportion of sepsis in ICU patients with AKI in our study was 60.89%. Sepsis was more commonly found in the non-survivor AKI group (92.27%). Among patients with AKI who developed sepsis, the proportion of co-morbid pulmonary disease was 51.82% (213 subjects) and the proportion of vasopressor drug use was 79.94% (308 subjects); moreover, the median of APACHE II score at admission was 11 with a range between 0 and 30. Our study found an association between sepsis and increased mortality among ICU patients with AKI. Our findings are in consistent with the results of studies conducted by Elhendy et al.[4], Zhou et al.[15], and Daher et al.[18] Those studies demonstrate that sepsis is a factor associated with increased mortality among ICU patients with AKI revealing OR of 13.75 (95%CI 1.68-112.02), OR of 4.55 (95%CI 1.037-19.87) and OR 4.79 (95%CI 1.88-12.17) respectively for each study.[4,15,18] Sepsis is a life-threatening organ dysfunction due to dysregulation of host response to infection.[12] The release of pro-inflammatory cytokines (IL-1, IL-6, TNF-) will lead to severe inflammatory reactions and multiple organ dysfunction that subsequently cause death.[19]

In our study, we found that the proportion of ventilator use was 67.26% among ICU patients with AK; while the proportion in the non-survivor AKI group was 91.82%. Among subjects in the AKI group who used mechanical ventilator, the proportion of pulmonary concomitant disease was 45.37% (206 subjects), the proportion of subjects with sepsis was 72.91% (331 subjects), the proportion of subjects using vasopressor drug was 69.16% (314 subjects) and the median APACHE II score at admission was 9. Our study found a significant association between ventilator use and increased AKI mortality in ICU. Similar results have also been demonstrated in the studies conducted by Daher et al.18, Medve et al.[20], and Zhou et al.[4], AKI can be induced by mechanical ventilator through 3 mechanisms. First, the presence of hypercapnia or hypoxemia can suppress blood flow to the kidneys. Second, increased intra-thoracic and intra-abdominal pressure will decrease cardiac output and eventually decrease blood flow to the kidneys. Third, the mechanical ventilator causes an inflammatory reaction in the lung that will induce the release of a systemic inflammatory mediator.[21]

The median for duration of ventilator use in our study was 2 days; however, in the non-survivor AKI group, the median was 7 days, which is longer than the median found in the survivor AKI group that was 1 day. Our study found a significant association between the duration of ventilator use and the increased mortality among ICU patients with AKI. A study conducted by Wang et al supports the results of our study. Thay found that 1 day longer duration of ventilator use will increase mortality by OR

of 1.08 (95%CI 1.008-1.158).[22] Longer duration of mechanical ventilator use will increase the risk of infection and mortality.[22] AKI alone may prolong the duration of mechanical ventilator use; thus further triggering trauma to the lungs and difficult extubating.[23,24]

The proportion of dialysis in our study was 10.96%. The proportion of AKI subjects undergoing dialysis was more commonly found in the non-survivor group than in the survivor group (21.36% vs. 5.93%). Based on the degree of AKI in the non-survivor AKI group, we found that the proportion of subjects using dialysis was 29.79% in AKI I, 19.15% in AKI II and 51.06% in AKI III. In our study, the bivariate analysis demonstrated a significant association between dialysis and increased mortality among ICU patients with AKI (RR 2.206; 95%CI 1.782-2.732). However, the multivariate analysis found no significant association with OR 1.034 (95%CI 0.419-2.555). In this study, dialysis served as a therapeutic factor in AKI; moreover, the proportion of AKI severity in this study was dominated by AKI I (72.15%). Dela Cruz et al.[24] have also found a meaningless association between dialysis and increased mortality among ICU patients with AKI using the bivariate analysis.

Our study found that the proportion of oligoanuria was 15.94%. The proportion of AKI subjects with oligoanuria was more common in the non-survivor AKI group (34.17%) than the survivor AKI group (8.5%). Based on the severity of AKI in the non-survivor AKI group, the proportion of oligoanuria was 39.02% in AKI I, 19.51% in AKI II, and 41.46% in AKI III. We found that the more severe the severity of AKI, the greater the proportion of subjects with oligoanuria. Our study also found a significant association between oligoanuria and increased mortality among ICU patients with AKI. The findings are supported by studies conducted by Elhendy et al.[15] (OR of 9.4 [95%CI 1.909-46.27]) and Daher et al.[18] (OR 5.59 [95%CI 1.83-17.07]). Patients with AKI who had oligoanuria had worse prognosis than those with non-oligouria AKI. Two possible underlying mechanisms are (1) the degree of severity of parenchymal structural changes is found to be greater in the oligoanuria AKI and (2) oligoanuria is more common in multiple organ failure conditions and critical illnesses that underlie the occurrence of AKI.[25] The median APACHE II score at admission in our study was 8. The score was greater in the non-survivor AKI group compared to the score in survivor AKI group (11 vs. 7). Based on the degree of AKI severity in the non-survivor AKI group, the median APACHE II score at admission was 9.5 in AKI I, 13 in AKI II, and 13.5 in AKI III.

The above mentioned results show that the non-survivor AKI group had a greater degree of disease severity. Furthermore, the more severe the severity of AKI, the greater the median APACHE II score at admission. In our study we found a significant correlation between APACHE II score at admission and increased mortality among ICU patients with AKI. Our findings are supported by results of studies conducted by Wang et al and Daher et al, that show similar results with OR 1.072 (95%CI 1.037-1.109) and OR 1.14 (95%CI 1.05-1.23), respectively.[18,22]

Our study is the first study conducted in Indonesia on factors associated with mortality among ICU patients with AKI. Unlike the previous studies, we involved subjects with a variety of characteristics including medical and surgical history including burns, acute heart disease and trauma. At last, the diagnosis of AKI is re-established and we found a discrepancy of AKI diagnosis as much as 29.48%.

Our study has several limitations. First, it was retrospective, in which the data were obtained from medical records and EHR system at Cipto Mangunkusumo National Central General Hospital and therefore, there were some incomplete data (oligoanuria, APACHE II score at admission, blood gas analysis, potassium serum level); however, those did not affect the results of our study. Second, the exclusion of CKD was performed based on supporting data (renal ultrasound and plasma creatinine level), which were obtained from medical records and EHR system at Cipto Mangunkusumo National Central General Hospital.

CONCLUSION

The prevalence of AKI in ICU patients at Cipto Mangunkusumo National Central General

Hospital was not high; however, the mortality rate of ICU patients with AKI was high. Sepsis, oligoanuria, ventilator, APACHE II score at admission and duration of ventilator use were significantly associated with increased mortality rate among ICU patients with AKI at Cipto Mangunkusumo Hospital.

CONFLICT OF INTEREST

There is no conflict of interest in this study. The research was fully funded by the researchers.

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