의학석사 학위논문

Post-discharge long-term prognosis of intensive care unit survivors who underwent renal replacement therapy

신대체요법을 받은 중환자실 생존자의 장기 예후

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이 수 진

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이 논문을 의학석사 학위논문으로 제출함

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Abstract

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Background : Dialysis requiring acute kidney injury (AKI-D) is known to worsen in-hospital mortality of intensive care unit (ICU) patients. Nevertheless, the long-term prognoses including major adverse cardiovascular events (MACE) among the post-discharge ICU patients who survived after AKI-D had not been previously investigated yet.

Methods : This is a nationwide, population-based cohort study using the claims data from Korean National Health Insurance System. All ICU admission events in Korean tertiary hospitals between 2006 and 2015 were considered. Patients under age of 20 or received any forms of dialysis before the index admission were excluded. AKI-D group consisted of ICU patients who

underwent dialysis and the control group included those who did not undergo dialysis during the index ICU admission. Additional analyses were performed specifically among the patients who received cardiac surgery or liver transplantation during the index admission.

Results : A total of 12,380 patients were in AKI-D group and 382,018 were in the control group. Long-term post-discharge mortality [adjusted hazard ratio (HR) 1.32 (1.26-1.39), P<0.001], progression to end-stage renal disease [adjusted HR 18.11 (15.78-20.79), P<0.001], and risk of MACE [adjusted HR 1.46 (1.32-1.62), P<0.001] were increased in AKI-D group, compared to the control group. Poor long-term prognosis were also observed among the post discharge patients who underwent dialysis following the cardiac surgery or liver transplantation.

Conclusion : AKI-D was associated with overall poor long-term prognoses. Thus, it is crucial for the clinicians to pay longitudinal attention to the elevated risk of adverse events among the post-discharge ICU patients who survived after

AKI-D.

Keyword : acute kidney injury, renal replacement therapy, intensive care unit

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Chapter 1. Introduction

1.1 Study background

Dialysis requiring acute kidney injury (AKI-D) is commonly complicated to critically ill patients during intensive care unit (ICU) admissions (1). Development of dialysis enabled to adjust renal replacement therapy (RRT) properly to critically ill patients to manage AKI-D, who are often accompanied with hemodynamic instability (2, 3). Despite the improvement in dialysis, the incidence of AKI-D is increasing (4), and it is still associated with poor post-discharge mortality (5, 6). Further investigations regarding the long-term post-discharge outcomes among the ICU survivors were mandatory.

Considering the organ interrelation with heart (7, 8) or liver (9, 10), dysfunctions of either organ may lead to subsequent renal insufficiency. AKI-D following the cardiac surgery or liver transplantation is both known to significantly worsen the in-hospital mortality (11). Although short-term survival after surgery had been improved over time (12, 13), AKI-D

developed among these patients continuously possess considerable medical burden. Thus, it is essential to assess the long-term outcomes of post-discharge patients who survived after AKI-D, to provide appropriate medical care after hospital discharge.

1.2 Purpose of the study

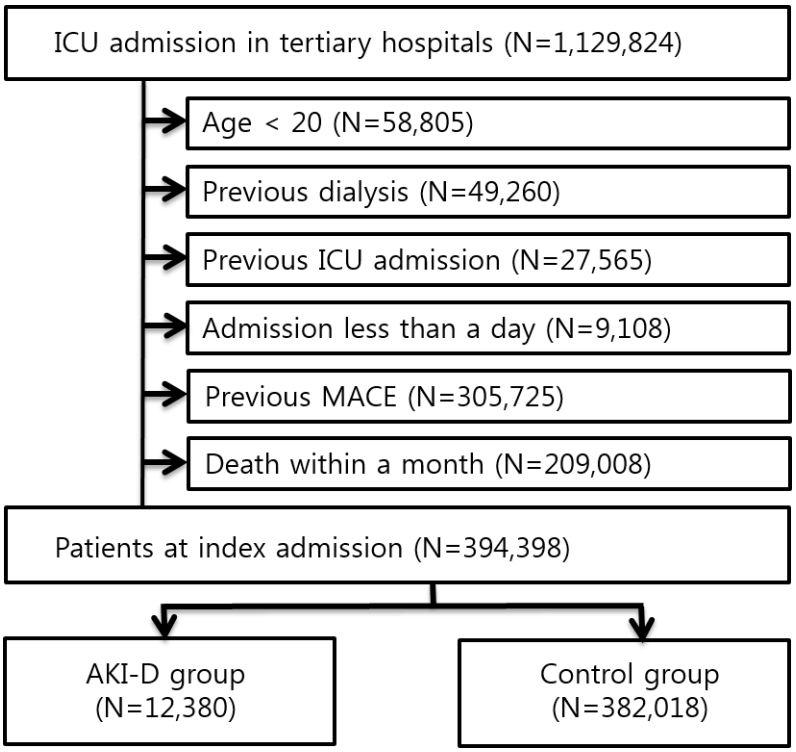
Herein, the present nationwide population-based cohort study was performed to investigate the post-discharge long-term prognoses of ICU patients who survived after AKI-D. All-cause mortality, risk of MACE development and risk of progression to end-stage renal disease (ESRD) were examined to demonstrate whether the outcomes differed on the requirement or modality of dialysis. Also, overall outcomes specifically among the patients underwent cardiac surgery or liver transplantation were examined to determine the distinct outcomes associated with AKI-D following the major surgery.

Chapter 2. Materials and Methods

2.1 Study design and participants

This study was a nationwide, population-based cohort study using the database of Korean National Health Insurance System (NHIS). NHIS collects and provides all insured medical service to Korean Nationality. Adult patients older than 20 years old who admitted to ICU in all tertiary hospitals in Korea between 2006 and 2015 were considered. Patients who previously admitted to ICU, experienced MACE within 3 years from the index admission or received any forms of RRT before the index admission were excluded. If the patients were issued with multiple ICU admissions, only the first event was considered for the index admission. Also, patients who expired within a month of index admission were excluded, to assess the long-term outcomes. (Figure 1)

Figure 1. The study flow diagram.



ICU = intensive care unit; MACE = major adverse cardiovascular event

Study participants were divided into two groups. Patients who underwent RRT during the index admission consisted AKI-D group, and those who did not undergo RRT were in control group. Among the study group, patients who received continuous renal replacement therapy (CRRT) for more than 24 hours were

considered as CRRT group, and the remaining were considered as intermittent renal replacement therapy (IRRT) group.

Among the study participants, patients underwent cardiac surgery or liver transplantation were separately examined for outcome analyses. The cardiac surgery included coronary artery bypass graft surgery with or without the application of cardiopulmonary bypass and open-heart valve replacement or repair surgery. The liver transplantation considered both living donor and deceased donor liver transplantation.

2.2 Data collection

From the NHIS database, claims data including medication use, past medical history, and principal diagnosis during the index admission were collected. Comorbidities were defined when the diagnosis codes were issued more than twice a year within the three years from the year of index admission. Then, they were described using the Charlson-comorbidity index (CCI) (14) and the International Classification of Disease (ICD)-10 codes (15).

Treatment modalities during ICU admission including the application status of mechanical ventilator and use of intravenous vasopressors were also collected for analysis.

2.3 Study outcomes

The primary outcome was all-cause long-term mortality. Risk of MACE development and progression to ESRD were also assessed. Among the liver transplantation recipients, risk of ICU re-admission and liver re-transplantation were additionally examined.

Death events were collected from Statistics Korea. Definition of MACE used issued ICD-10 codes as the following; acute myocardial infarction (MI) (ICD-10 code I21 or I22), revascularization (claims data of cardiovascular revascularization), and acute ischemic stroke (ICD-10 codes I63). Progression to ESRD was defined when a patient continued dialysis for more than 90 days after the hospital discharge.

Among the patients underwent cardiac surgery or liver transplantation, additional subgroup analyses were performed after exception of patients who continued dialysis at the hospital discharge, to minimize the effect of ESRD on long-term outcomes. Remaining patients who recovered from dialysis at the hospital discharge were grouped as renal recovery group and outcomes were compared to the control group.

2.4 Statistical analysis

To compare the difference of categorical variables, chi-squared test was used and the data were presented as frequencies (percentages). The non-normally distributed continuous variables were compared using Mann-Whitney U test and presented as median (interquartile ranges). The survival curves were obtained from the Kaplan-Meier method. The outcomes and *P*-values were analyzed from the log-rank test. Cox proportional hazard model was used for multivariable regression analysis and the following variables were considered;

age, sex, and CCI. Cox regression and backward-elimination approach were used for assessment of risk factors for MACE.

The result table contains 3 columns. Model 1 presents an unadjusted univariate analysis. Model 2 presents the values adjusted for age, sex, CCI, application status of a mechanical ventilator, usage of inotropic agents, and the principal diagnosis of the index admission. Model 3 presents the results from 1:1 propensity-score-matched dataset using the matching variables including age, sex, comorbidities and principal diagnosis during the index admission. Then, multivariable Cox regression analyses were applied using the variables used in Model 2.

A two-sided *P*-value under 0.05 was considered to be statistically significant. All analyses were performed with SAS 9.4 program (SAS Institute, United States).

2.5 Ethical consideration

The study was approved by the Institutional Review Board of Seoul National University Hospital (E-1711-040-897). Access to NHIS database was approved by the designated government

department. Informed consent was waived as it was a retrospective study without any additional medical intervention to participating patients. The study was performed in accordance with the latest version of declaration of Helsinki throughout the study period.

Chapter 3. Results

3.1 Study population

A total of 1,129,824 patients admitted to ICU between January 2005 and December 2016 and 394,398 patients satisfied the inclusion criteria. Among them, 12,380 patients underwent dialysis during the index ICU admission and grouped as AKI-D group. The remaining 382,018 patients who did not undergo dialysis were in the control group. In AKI-D group, 6,891 patients underwent CRRT and 5,034 received IRRT. The median follow-up duration among the total AKI-D group were 3.55 (1.33-6.75) years.

3.2 Baseline characteristics

The baseline characteristics of the total AKI-D and control groups are presented in Table 1. The characteristics between two groups were differently distributed. AKI-D group patients were younger ($P<0.001$) and more commonly male gender ($P<0.001$) than the control group. Mechanical ventilator

(P<0.001) and intravenous inotropic agents (P<0.001) were more frequently applied in the AKI-D group.

Table 1. Baseline characteristics of study participants.

Variables	AKI-D group (N=12,380)	Control group (N=382,018)	*P* value
Age (years) (years (interquartile ranges))	57 (45-69)	59 (47-70)	<0.001
< 40 (N, %)	2,101 (17.0)	54,745 (14.3)	
≥ 40 and < 60 (N, %)	4,811 (38.9)	143,346 (37.5)	
≥ 60 and < 80 (N, %)	4,667 (37.7)	158,527 (41.5)	
≥ 80 (N, %)	801 (6.5)	25,400 (6.7)	
Male sex (N, %)	7,337 (59.3)	222,311 (58.2)	0.017
Era of admission (N, %)			<0.001
2015~	3,041 (24.6)	133,887 (35.1)	
2010~2014	6,044 (48.8)	173,455 (45.4)	
2005~2009	3,295 (26.6)	74,676 (19.6)	
Charlson Comorbidity Index score (N, %)	2 (0-4)	1 (0-3)	<0.001
≥ 0 and < 5	10,986 (88.7)	363,858 (95.3)	
≥5 and <10	1,337 (10.8)	17,625 (4.6)	
≥ 10	57 (0.5)	535 (0.1)	
Implemented treatment during ICU admission (N, %)			

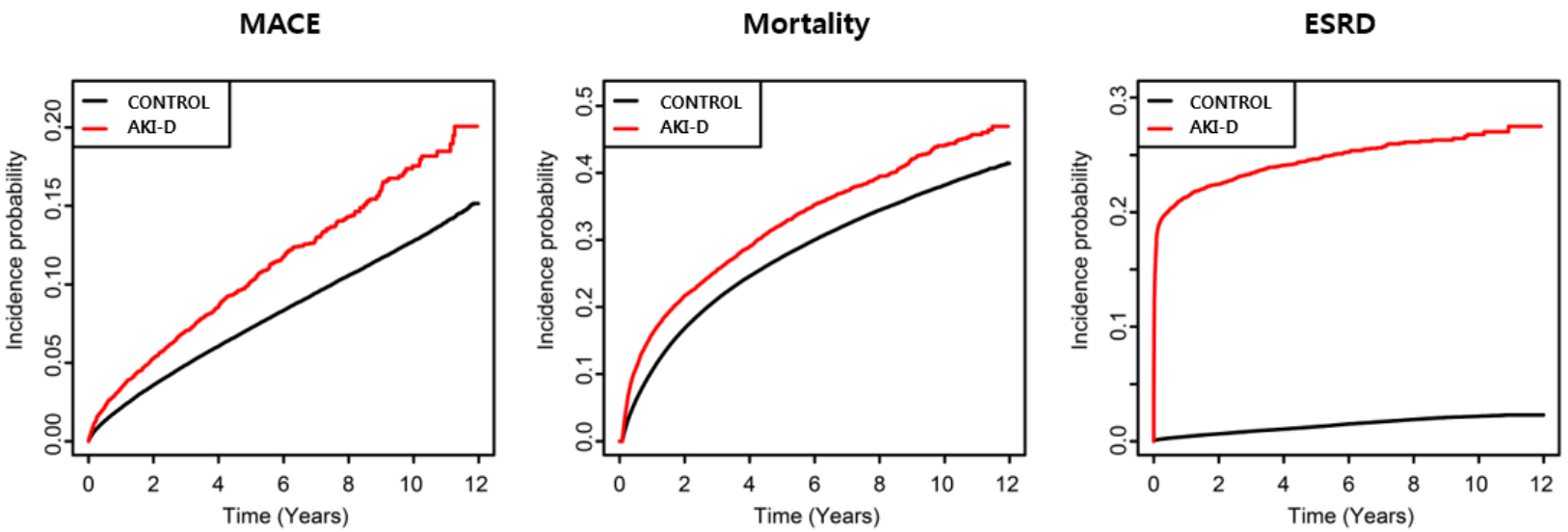
Ventilator care	6,275 (50.7)	102,616 (26.9)	<0.001
Intravenous inotropic agents	7,934 (64.1)	161,963 (42.4)	<0.001

ICU = intensive care unit, MACE = major adverse cardiovascular event, MI = myocardial infarction, ESRD = end-stage renal disease

3.3 Outcomes of the total AKI-D patients

In total AKI-D group, all-cause mortality, risk of MACE and risk of progression to ESRD within and after 90 days from the discharge were higher, compared to the control group (Figure 2). The poor prognoses among the AKI-D group were repeatedly consistent after multivariate adjustment and the analyses among the propensity score matched dataset (Table 2).

Figure 2. The Kaplan-Meier survival curves of the study outcomes in total AKI-D group.



The x-axes indicate the time (years), and the y-axes indicate the incidence probability.

Table 2. Clinical outcomes of total AKI-D group

	Model 1		Model 2		Model 3	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Total AKI-D (N = 12,380) vs. Control (N = 382,018) group						
Mortality	1.27 (1.23-1.32)	<0.001	1.34 (1.30-1.39)	<0.001	1.32 (1.26-1.39)	<0.001
Within 90 days	2.12 (1.97-2.28)	<0.001	1.80 (1.66-1.94)	<0.001	1.63 (1.44-1.85)	<0.001
After 90 days	1.15 (1.11-1.19)	<0.001	1.25 (1.20-1.30)	<0.001	1.27 (1.20-1.34)	<0.001
MACE	1.45 (1.36-1.55)	<0.001	1.29 (1.21-1.39)	<0.001	1.46 (1.32-1.62)	<0.001
Within 90 days	1.83 (1.57-2.13)	<0.001	1.47 (1.25-1.74)	<0.001	1.62 (1.27-2.07)	<0.001
After 90 days	1.39 (1.29-1.49)	<0.001	1.26 (1.16-1.35)	<0.001	1.43 (1.28-1.60)	<0.001
Acute MI	1.60 (1.42-1.79)	<0.001	1.38 (1.22-1.56)	<0.001	1.35 (1.14-1.61)	<0.001
Revascularization	1.82 (1.49-2.22)	<0.001	1.45 (1.17-1.80)	0.007	1.62 (1.19-2.20)	0.002

Acute ischemic stroke	1.33 (1.21−1.45)	<0.001	1.22 (1.11−1.34)	<0.001	1.51 (1.31−1.73)	<0.001
Progression to ESRD	28.96 (27.59−30.38)	<0.001	10.75 (10.12−11.42)	<0.001	18.11 (15.78−20.79)	<0.001
Within 90 days	113.02 (104.02−122.79)	<0.001	34.49 (31.15−38.20)	<0.001	50.66 (39.35−65.21)	<0.001
After 90 days	6.33 (5.72−7.00)	<0.001	3.09 (2.77−3.44)	<0.001	4.96 (4.10−5.99)	<0.001

HR = hazard ratio, CI = confidence interval, MACE = major adverse cardiovascular event, MI = myocardial infarction, ESRD = end−stage renal disease

Model 1 was an unadjusted simple model.

Model 2 was adjusted for age, sex, the Charlson Comorbidity Index scores, usage of mechanical ventilation, use of intravenous inotropic agents, and principal diagnosis during the index admission (categorical, the most common six alphabetical ICD−10 diagnostic codes (A, C, I, J, K, N), and others)

Model 3 was a multivariable Cox regression analysis performed in the 1:1 propensity score matched dataset [AKI−D (N = 12,380) vs. matched control (N = 12,380)]. The multivariable analysis was adjusted for all variables included in Model 2.

3.4 Outcomes of the total AKI-D patients according to the dialysis modality

When comparing the prognoses according to the implemented dialysis modality in total AKI-D group, all-cause mortality was increased in patients who received CRRT, but the risk of progression to ESRD was elevated with IRRT. The risk of MACE development was not different, regardless of the implemented dialysis modality, even after the multivariate adjustment [adjusted HR 1.05 (95% CI 0.89-1.24), P=0.575] (Table 3).

Table 3. Clinical outcomes of AKI-D group according to specific acute renal replacement therapy modality and renal recovery.

	Model 1		Model 2		Model 3	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
CRRT (N = 6,891) vs. IRRT (N = 5,034) group						
MACE	1.04 (0.91-1.18)	0.616	1.06 (0.91-1.23)	0.449	1.05 (0.89-1.24)	0.575
Acute MI	0.97 (0.77-1.22)	0.810	0.98 (0.75-1.27)	0.867	0.99 (0.75-1.31)	0.942
Revascularization	0.88 (0.59-1.31)	0.528	1.07 (0.68-1.67)	0.785	1.13 (0.69-1.84)	0.631
Acute ischemic stroke	1.11 (0.92-1.33)	0.252	1.12 (0.91-1.37)	0.282	1.08 (0.86-1.36)	0.503
Mortality	1.20 (1.12-1.28)	<0.001	1.09 (1.01-1.18)	0.031	1.12 (1.03-1.22)	0.010
Progression to ESRD	0.33 (0.30-0.35)	<0.001	0.42 (0.38-0.45)	<0.001	0.44 (0.40-0.48)	<0.001

HR = hazard ratio, CI = confidence interval, MACE = major adverse cardiovascular event, MI = myocardial infarction, ESRD = end-stage renal disease, CRRT = continuous renal replacement therapy, IRRT = intermittent renal replacement therapy

Hazard ratios and confidence intervals of the CRRT group were computed using the IRRT group as the reference group in the

Cox regression analysis.

Model 1 was an unadjusted simple model.

Model 2 was adjusted for age, sex, the Charlson Comorbidity Index scores, usage of mechanical ventilation, use of intravenous inotropic agents, and the principal diagnosis during the index admission (categorical, the most common six alphabetical ICD-10 diagnostic codes (A, C, I, J, K, N), and others)

Model 3 was a multivariable Cox regression analysis performed in the 1:1 propensity score matched dataset [matched CRRT (N = 4,789) vs. matched IRRT (N = 4,789)]. The model was adjusted for all variables included in Model 2.

3.5 Clinical factors associated with MACE in total AKI-D patients

Old age [adjusted HR 1.04 (95% CI 1.04-1.05), P<0.001] and male gender [adjusted HR 1.18 (95% CI 1.04-1.36), P=0.014] were associated with increased risk of MACE in total AKI-D patients. In addition, underlying diabetes [adjusted HR 1.27 (95% CI 1.08-1.49), P=0.003], diabetic complications [adjusted HR 1.64 (95% CI 1.36-1.98), P<0.001], heart failure [adjusted HR 1.34 (95% CI 1.07-1.66), P=0.009], peripheral vascular disease [adjusted HR 2.45 (95% CI 1.01-5.94), P=0.047], and renal disease [adjusted HR 1.35 (95% CI 1.15-1.60), P<0.001] were significantly associated with elevated risk of MACE development in AKI-D patients (Table 4).

Table 4. Clinical characteristics associated with MACE in the total AKI-D group

	Multiple cox		Backward	
Age	1.04 (1.03-1.05)	<0.001	1.04 (1.04-1.05)	<0.001
Male sex	1.20 (1.04-1.37)	0.011	1.18 (1.04-1.36)	0.014
Comorbidities (CCI)				
Hypertension	1.08 (0.91-1.29)	0.365		
Diabetes	1.25 (1.06-1.47)	0.009	1.27 (1.08-1.49)	0.003
Diabetic complication	1.63 (1.35-1.97)	<0.001	1.64 (1.36-1.98)	<0.001
Connective tissue disease	1.12 (0.77-1.63)	0.564		
Congestive heart failure	1.33 (1.06-1.65)	0.013	1.34 (1.07-1.66)	0.009
Peripheral vascular disease	1.09 (0.86-1.39)	0.463	2.45 (1.01-5.94)	0.047
Pulmonary disease	1.07 (0.91-1.25)	0.417		
Peptic ulcer	1.09 (0.94-1.28)	0.259		
Liver disease	0.91 (0.56-1.46)	0.064		
Severe liver disease	0.59 (0.34-1.03)	0.062		
Renal Disease	1.33 (1.12-1.57)	0.001	1.35 (1.15-1.60)	<0.001
Cancer	1.01 (0.76-1.35)	0.925		
Metastatic cancer	0.75 (0.40-1.40)	0.367		
Principal diagnosis, ICD-10 alphabetical index				

Certain infectious and parasitic diseases	A	1.03 (0.68−1.55)	0.887	1.08 (0.75−1.54)	0.680
	B	0.42 (0.14−1.21)	0.108	0.49 (0.18−1.33)	0.160
Neoplasms or hematological diseases	C	Reference		Reference	
	D	1.08 (0.56−2.08)	0.830	1.14 (0.61−2.15)	0.683
Endocrine nutritional and metabolic diseases	E	1.51 (0.95−2.39)	0.082	1.59 (1.06−2.40)	0.027
Mental and behavioral diseases	F	0.988 (0.307−	0.985	1.04 (0.33−3.30)	0.947
Diseases of the nervous system	G	2.96 (1.61−5.45)	0.001	3.12 (1.76−5.52)	<0.001
Diseases of the circulatory system	I	1.74 (1.21−2.49)	0.003	1.82 (1.38−2.41)	<0.001
Diseases of the respiratory system	J	1.50 (1.01−2.23)	0.045	1.64 (1.17−2.29)	0.004
Diseases of the digestive system	K	0.97 (0.66−1.42)	0.886	0.96 (0.70−1.33)	0.827
Diseases of the skin and subcutaneous tissue	L	0.47 (0.06−3.43)	0.456	0.51 (0.07−3.64)	0.498
Diseases of the muscle and connective tissue	M	1.91 (1.20−3.04)	0.006	2.05 (1.35−3.11)	0.001
Diseases of the genitourinary system	N	1.29 (0.93−1.79)	0.124	1.38 (1.07−1.78)	0.013
Implemented treatment modalities					
Ventilator care		1.11 (0.95−1.31)	0.180		
Intravenous inotropic agents		0.87 (0.75−1.02)	0.093		

MACE = major adverse cardiovascular event, CCI = Charlson comorbidity index, ICD = International Classification of Disease−10

3.6 Comparison of the outcomes among the patients received cardiac surgery

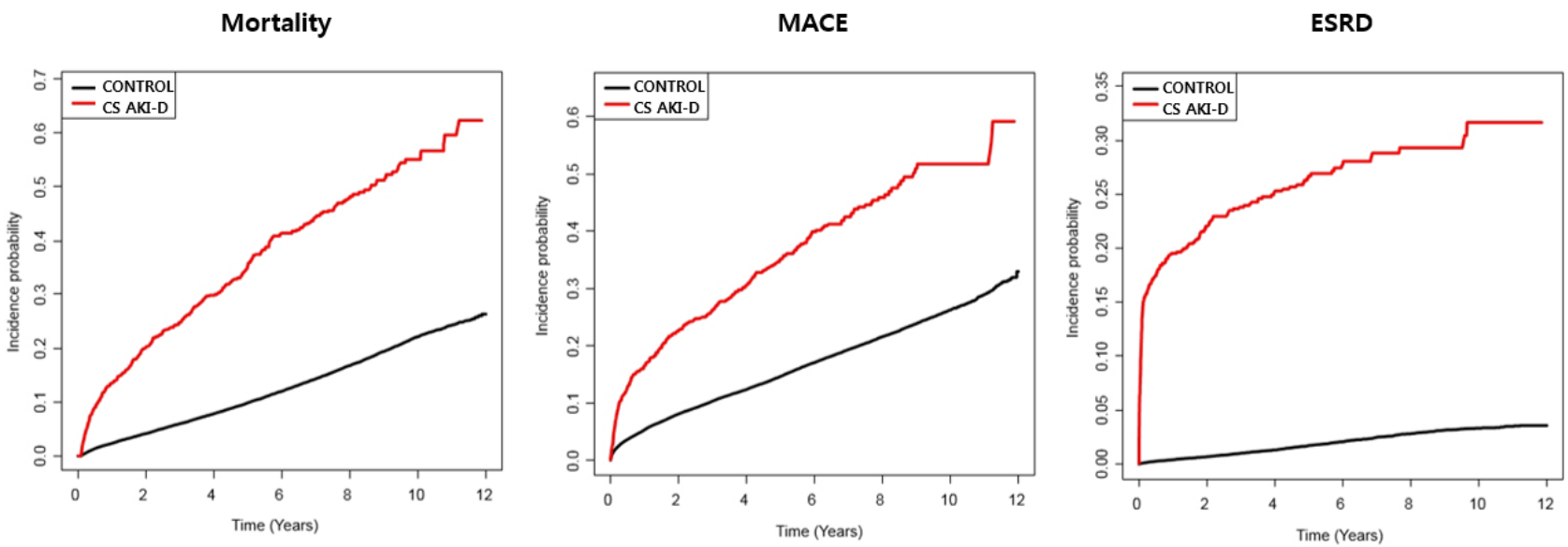
A total of 1,261 patients underwent dialysis during the ICU admission following cardiac surgery (CS AKI-D). The prognoses of CS AKI-D group were compared to 43,847 patients in the control group.

CS AKI-D group exhibited overall poor prognoses compared to the control group (Figure 3). In CS AKI-D group, 445 patients (35.3%) died and 393 patients (31.7%) developed MACE after the hospital discharge. CS AKI-D group showed worse short-term [adjusted HR 5.76 (4.33-7.68, P<0.001)] and long-term all-cause mortality [adjusted HR 2.72 (2.44-3.02), P<0.001] than the control group. CS AKI-D patients showed increased risk of MACE, both within [adjusted HR 3.56 (2.93-4.32), P<0.001] and after [adjusted HR 1.97 (1.75-2.23), P<0.001] 90 days from the hospital discharge. The risk of ESRD progression was also elevated in the CS AKI-D group [adjusted hazard ratio (HR) 15.59 (13.89-18.33), P<0.001]. The overall outcomes of the CS AKI-D group remained consistent after multivariate adjustment

and comparisons in the propensity-score-matched groups.

Additional subgroup analyses were performed in CS AKI-D group, after exception of the patients who continued dialysis at the time of hospital discharge. The renal recovery patients continuously showed worse all-cause mortality [adjusted HR 2.38 (2.13-2.66), P<0.001] and elevated risks of composite MACE [adjusted HR 1.73 (1.54-1.95), P<0.001] than the control group (Table 5).

Figure 3. The Kaplan-Meier survival curves of the study outcomes in CS AKI-D group.



The x-axes indicate the time (years), and the y-axes indicate the incidence probability.

Table 5. Clinical outcomes of the AKI-D patients who underwent cardiac surgery

	Model 1		Model 2		Model 3	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
CS AKI-D (N = 1,261) vs. Control (N = 43,847) group						
Mortality	3.99 (3.63-4.40)	<0.001	2.93 (2.65-3.23)	<0.001	2.91 (2.46-3.45)	<0.001
Within 90 days	8.33 (6.32-10.98)	<0.001	5.76 (4.33-7.68)	<0.001	4.61 (2.58-8.25)	<0.001
After 90 days	3.69 (3.33-4.10)	<0.001	2.72 (2.44-3.02)	<0.001	2.76 (2.31-3.30)	<0.001
MACE	2.75 (2.48-3.04)	<0.001	2.26 (2.04-2.51)	<0.001	2.31 (1.96-2.73)	<0.001
Within 90 days	3.96 (3.28-4.78)	<0.001	3.56 (2.93-4.32)	<0.001	4.05 (2.72-6.02)	<0.001
After 90 days	2.43 (2.16-2.75)	<0.001	1.97 (1.75-2.23)	<0.001	2.00 (1.66-2.41)	<0.001
Non-fatal MI	3.84 (3.32-4.44)	<0.001	3.12 (2.69-3.62)	<0.001	3.11 (2.40-4.05)	<0.001
Revascularization	0.89 (0.57-1.41)	0.630	0.81 (0.51-1.28)	0.359	1.12 (0.61-2.07)	0.717
Acute ischemic stroke	2.52 (2.17-2.93)	<0.001	2.03 (1.74-2.37)	<0.001	1.99 (1.57-2.52)	<0.001

Progression to ESRD	20.09 (17.57–22.96)	<0.001	15.95 (13.89–18.33)	<0.001	13.07 (8.96–19.05)	<0.001
Renal recovery (N = 1,099) vs. Control (N = 43,815) group						
Mortality	3.20 (2.87–3.57)	<0.001	2.38 (2.13–2.66)	<0.001	2.58 (2.13–3.13)	<0.001
MACE	2.06 (1.84–2.32)	<0.001	1.73 (1.54–1.95)	<0.001	2.00 (1.66–2.42)	<0.001
Non–fatal MI	2.64 (2.21–3.14)	<0.001	2.18 (1.82–2.60)	<0.001	2.71 (1.99–3.70)	<0.001
Revascularization	0.41 (0.22–0.76)	0.005	0.39 (0.21–0.74)	0.004	0.49 (0.23–1.05)	0.067
Acute ischemic stroke	2.18 (1.85–2.57)	<0.001	1.78 (1.51–2.11)	<0.001	1.97 (1.52–2.55)	<0.001

MACE = major adverse cardiovascular event, MI = myocardial infarction, ESRD = end–stage renal disease, HR = hazard ratio, CI = confidence interval

Model 1 was an unadjusted simple model.

Model 2 was adjusted for age, sex, the Charlson Comorbidity Index scores, use of mechanical ventilation, use of intravenous inotropic agents, and principal diagnosis during the index admission (categorical, the most common six alphabetical ICD–10 diagnostic codes (A, C, I, J, K, N), and others)

Model 3 was a multivariable Cox regression analysis performed in the 1:1 propensity score matched dataset [AKI–D (N = 1,258)

vs. matched control (N = 1,258)]. The multivariable analysis was adjusted for all variables included in Model 2. Model 3 of renal recovery group was a multivariable Cox regression analysis performed in the 1:1 propensity-score-matched dataset [CS AKI-D (N = 1,098) vs. matched control (N = 1,098)]. The multivariable analysis was adjusted for all variables included in Model 2.

3.7 Comparison of the outcomes among the patients received liver transplantation.

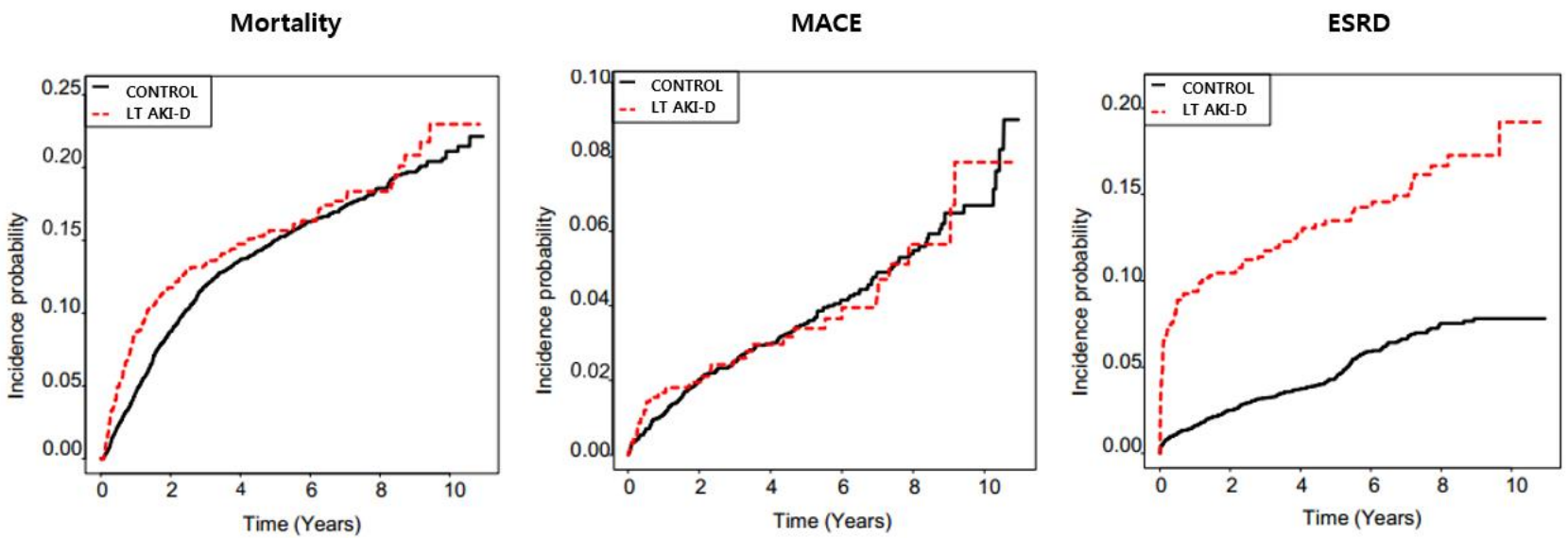
Of 6,879 patients who received liver transplantation, 968 patients received dialysis during the index admission and grouped as LT AKI-D group. Then, the outcomes were compared to the remaining 5,911 patients in the control group.

Overall prognoses were increased in LT AKI-D group (Figure 4). LT AKI-D group patients showed increased short-term [adjusted HR 4.43 (2.58-7.62), P<0.001] and long-term [adjusted HR 1.36 (1.11-1.65), P=0.003] mortality. LT AKI-D group patients were associated with increased risk of ESRD progression [adjusted HR 2.93 (2.34-3.66), P<0.001]. Also, LT AKI-D group patients showed higher rate of ICU re-admission and it was consistently increased after the multivariate adjustment [adjusted HR 1.70 (1.44-2.01), P<0.001]. In contrast, the rate of liver re-transplantation among the post-discharge patients was not different between the two groups, even after the multivariate adjustment [adjusted HR 1.59 (0.95-2.66), P=0.076] and after the propensity score-matched group

analysis [adjusted HR 1.37 (0.71−2.65), P=0.344]. The risk of MACE development in AKI−D group was comparable between two groups [adjusted HR 1.17 (0.80−1.70), P=0.430].

The patients in LT AKI−D group who recovered from dialysis at the hospital discharge were separately grouped for additional subgroup analysis. The post−discharge patients who recovered from dialysis showed significantly worse short−term post−discharge mortality compared to the control group [HR 3.24 (1.94−5.44), P<0.001]. However, the long−term mortality of the renal recovery group patients was not different to that of the control group [HR 0.94 (0.77−1.15), P=0.536]. The overall risk of short− and long−term ESRD progression, the rate of ICU re−admission, the risk of MACE and risk of re−transplantation in the renal recovery group were similar to those of the LT AKI−D group patients. All results were repeatedly consistent after the multivariate adjustment and the analysis among the propensity−score matched group (Table 6).

Figure 4. The Kaplan-Meier survival curves of the study outcomes in LT AKI-D group.



The x-axes indicate the time (years), and the y-axes indicate the incidence probability.

Table 6. Clinical outcomes of the AKI-D patients who underwent liver transplantation

	Model 1		Model 2		Model 3	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
LT AKI-D (N = 968) vs. Control (N = 5,911) group						
Mortality	1.14 (0.95-1.36)	0.162	1.52 (1.26-1.83)	<0.001	1.73 (1.32-2.26)	<0.001
Within 90 days	3.28 (1.98-5.44)	<0.001	4.43 (2.58-7.62)	<0.001	7.56 (2.25-25.48)	0.001
After 90 days	1.01 (0.83-1.22)	0.920	1.36 (1.11-1.65)	0.003	1.51 (1.13-2.00)	0.005
MACE	1.03 (0.71-1.49)	0.876	1.17 (0.80-1.70)	0.430	0.99 (0.61-1.61)	0.970
Within 90 days	1.27 (0.49-3.33)	0.625	1.33 (0.50-3.58)	0.569	2.24 (0.42-11.91)	0.344
After 90 days	1.00 (0.67-1.48)	0.983	1.16 (0.77-1.75)	0.484	0.90 (0.54-1.51)	0.698
Non-fatal MI	0.70 (0.28-1.78)	0.457	0.64 (0.25-1.66)	0.362	0.46 (0.16-1.34)	0.154
Revascularization	1.17 (0.55-2.49)	0.685	1.54 (0.7-3.38)	0.283	0.92 (0.34-2.48)	0.863

Acute ischemic stroke	1.11 (0.69−1.78)	0.682	1.26 (0.77−2.06)	0.363	1.39 (0.71−2.71)	0.339
Progression to ESRD	3.22 (2.60−3.99)	<0.001	2.93 (2.34−3.66)	<0.001	3.12 (2.21−4.41)	<0.001
Within 90 days	8.72 (6.06−12.54)	<0.001	7.44 (5.07−10.92)	<0.001	12.53 (5.38−29.16)	<.0001
After 90 days	1.81 (1.341−2.44)	<0.001	1.69 (1.24−2.30)	<0.001	1.64 (1.08−2.49)	0.020
ICU re−admission	1.59 (1.35−1.87)	<0.001	1.70 (1.44−2.01)	<0.001	1.61 (1.27−2.03)	<0.001
Within 90 days	1.94 (1.47−2.56)	<.0001	2.01 (1.51−2.68)	<.0001	1.99 (1.30−3.04)	0.001
After 90 days	1.44 (1.18−1.76)	0.0003	1.58 (1.28−1.94)	<.0001	1.46 (1.11−1.94)	0.008
Re−transplantation	1.84 (1.13−3.00)	0.014	1.59 (0.95−2.66)	0.076	1.37 (0.71−2.65)	0.344
Renal recovery (N = 918) vs. Control (N = 5,880) group						
Mortality	1.08 (0.90−1.30)	0.417	1.33 (1.10−1.61)	0.003	1.46 (1.11−1.91)	0.007
Within 90 days	3.28 (1.97−5.46)	<0.001	3.66 (2.15−6.23)	<0.001	7.72 (2.29−26.00)	0.001
After 90 days	0.94 (0.77−1.15)	0.536	1.17 (0.95−1.43)	0.143	1.25 (0.94−1.66)	0.132
MACE	0.93 (0.63−1.37)	0.713	1.11 (0.75−1.65)	0.589	1.51 (0.86−2.67)	0.154
Progression to ESRD	2.22 (1.70−2.89)	<0.001	2.20 (1.68−2.89)	<0.001	1.92 (1.31−2.83)	<0.001

ICU re-admission	1.43 (1.21-1.69)	<0.001	1.59 (1.34-1.89)	<0.001	1.55 (1.22-1.98)	<0.001
Re-transplantation	1.62 (0.98-2.68)	0.059	1.53 (0.91-2.57)	0.109	1.58 (0.76-3.30)	0.223

MACE = major adverse cardiovascular event, MI = myocardial infarction, ESRD = end-stage renal disease, ICU = intensive care unit.

Model 1 was an unadjusted simple model.

Model 2 was adjusted for age, sex, the Charlson Comorbidity Index scores, usage of mechanical ventilation, use of intravenous inotropic agents, etiology of liver disease and principal diagnosis during the index admission (categorical, the most common six alphabetical ICD-10 diagnostic codes (A, C, I, J, K, N), and others)

Model 3 was a multivariable Cox regression analysis performed in the 1:1 propensity score matched dataset [LT AKI-D (N = 965) vs. matched control (N = 965), and matched renal recovery group (n=915) vs. matched control (n=915)]. The multivariable analysis was adjusted for all variables included in Model 2.

Chapter 4. Discussion

The present nationwide cohort study demonstrated that all-cause long-term mortality, risk of MACE development, and risk of progression to ESRD were significantly increased in ICU patients who survived after AKI-D. The poor prognoses associated with AKI-D were also observed in the patients who underwent cardiac surgery or liver transplantation during the index admission.

Despite known adverse effects of AKI on cardiovascular events (16, 17), long-term risk of MACE development among the ICU survivors who survived after AKI-D had not been previously examined. The major strengths of the study were that relatively large number of ICU patients were reviewed using the nationwide dataset and investigated increased risk of long-term MACE among these patients. Present study could be an evidence for the clinicians that longitudinal follow-up for long-term MACE are warranted among the post-discharge AKI-D patients. As traditional risk factors exhibited

independent association to the increased risk of MACE, ICU survivors with risk factors require closer monitoring.

In addition, the risk of MACE according to the dialysis modality was newly demonstrated. Improvement of dialysis enabled to properly treat AKI-D patients even with high medical acuity and the demand of CRRT is increasing (2, 18). Nevertheless, whether the long-term prognoses differ according to the dialysis modality had rarely been investigated. When compared in ICU survivors who underwent dialysis during the index ICU admission, long-term risk of MACE was comparable, regardless of the dialysis modality, despite high medical acuity of those who received CRRT.

Hemodynamic instability and volume overload during the perioperative period of cardiac surgery lead to frequent development of AKI (7, 19) and it is known to be associated with worsening the in-hospital mortality (20, 21). CS AKI-D group showed association with increased post-discharge long-term mortality, ESRD progression and MACE development compared to patients who did not undergo dialysis. The results

were consistent across patients, after exception of patients who continued dialysis at the hospital discharge. To reduce the independent effect of ESRD on poor patient mortality (22), additional analyses were performed among those who recovered from dialysis at the hospital discharge. Consistently elevated long-term mortality in renal recovery group patients supported the possibility of direct effect of AKI-D on long-term outcomes. To my knowledge, it was the first to report the long-term outcomes including MACE development in critically ill patients who required dialysis following the cardiac surgery. Clinicians need to be informed that regarding the longitudinal effect of AKI-D on adverse events, post-discharge ICU patients survived after temporary AKI-D following cardiac surgery continuously require closer attention after hospital discharge.

AKI-D is one of the common complications occurred during perioperative period of liver transplantation (23-25) and it is known to decrease in-hospital patient survival (11, 26). The study focused on the long-term impact of AKI-D on prognosis

among the patients received liver transplantation. AKI-D developed during the perioperative period of liver transplantation was associated with poor short-term and long-term mortality. Also, ESRD progression and ICU re-admission rate were also increased with experience of AKI-D. In contrast, possibility of MACE development and liver re-transplantation were not different according to the dialysis requirement. Similar to the subgroup analysis among the cardiac surgery patients, LT AKI-D patients also underwent subgroup analysis after exception of the patients who were continuously on dialysis at the hospital discharge. They showed overall similar outcomes as the LT AKI-D patients, however, long-term survival rate became comparable to the control group patients. Comparable long-term mortality between the groups could be explained by several theories. As majority of LT AKI-D patients recovered from dialysis at the discharge, temporary AKI-D may not have longitudinal impact on long-term mortality. In addition, low incidence of MACE in liver transplantation patients could be another explanation. Compared

to the rate of MACE development in total AKI-D patients (7.4 %), only 3.41 % of liver transplantation patients developed MACE. Relatively low incidence of MACE, which is well-known risk factor of patient mortality, may have led to comparable long-term mortality among the patients who completely recovered from dialysis.

There are several limitations that should be considered during the interpretation of the results as it was a retrospective study. The claims data of the Korean NHIS are accurately and sensitively collected. However, the complete medical records and laboratory exam results were not available in the dataset. Although multivariate adjustment and propensity-score-matching with extensive claims data were applied to minimize the differences in medical severity between the groups, baseline renal functions, hemodynamic change or complete surgical procedures during the admission period could not be considered. Also, as NHIS database became available after the year of 2002, some portion of patients' remote medical histories could not be considered.

Chapter 5. Conclusion

In conclusion, post-discharge ICU patients who survived after AKI-D exhibited poor short- and long-term mortality, increased risk of MACE development and ESRD progression compared to those who did not undergo dialysis. It is essential for the clinicians to consider longitudinal impact of AKI-D on long-term outcomes and carefully follow-up post-discharge ICU patients who underwent dialysis with possibility of increased risk of adverse outcomes.

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초 록

연구목적: 신대체요법을 요하는 중증 급성 신손상은 병원 내 사망률 증가와 연관되어 있다. 중환자실 환자들의 중증 급성 신손상을 치료하기 위하여 신대체요법을 적용하는 경우가 증가하고 있음에도 환자들의 장기적인 예후와 관련된 연구가 충분히 이루어 지지 않았다. 이에 중환자실에서 신대체요법을 시행 받은 후 퇴원한 환자들의 장기적인 예후에 대하여 연구해보고자 하였다.

연구방법: 우리나라 국민건강보험공단에 청구된 데이터를 이용하여 후향적 코호트를 구축하였고, 2006년부터 2015년 사이 3차 병원 중환자실에 입원하여 신대체요법을 시행 받은 병력이 있는 성인 환자들을 대상으로 장기 생존율 및 예후를 분석하였다. 여러 차례의 입원력이 있는 경우 첫 중환자실 입원을 대상으로 하였고, 입원 전 투석 병력이 있는 환자는 모두 제외하였다. 추가적으로, 주요 심장 수술 및 간 이식을 시행 받은 환자들을 대상으로 하위 집단 분석을 시행하였다.

결과: 연구 기간 동안 중환자실에 입실하였던 1,129,814명의 환자 중에서 입원 기간 중 신대체요법을 시행 받은 12,380명의 환자를 AKI-D 군, 시행 받지 않은 382,018명의 환자를 대조군에

배정하였다. 90일 이내 및 90일 이후의 사망, 주요 심혈관계 합병증, 만성 신부전으로의 진행률이 모두 AKI-D 군에서 유의하게 증가됨을 확인하였다. 투석을 시행하지 않은 군과 비교하여 AKI-D 군에서 유의하게 악화되는 예후는 심장 수술 및 간 이식을 시행 받은 하위 집단에서도 유사하게 관찰되었다.

결론: 투석을 요하는 중증 급성 신손상은 중환자실 환자들의 단기 및 장기 생존률 악화, 심혈관계 합병증 발생, 만성 신부전 진행 증가와 유의한 연관성을 보였다. 투석을 요하는 중증 급성 신손상이 중환자실 생존자들의 퇴원 후 예후에 장기적인 영향을 미치므로, 이들 생존자들을 대상으로 주의 깊은 장기적 추적관찰이 필요하겠다.

주요어: 급성 신손상, 신대체요법, 중환자실

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