의학석사 학위논문

3단계 급성 신장 장애를 동반한 외상 환자에서 지속적인 신대치요법 적용의 위험인자

Risk factors for persistent renal replacement therapy in trauma patients with stage 3 acute kidney injury patients

울산대학교 대학원

의학과

최 경 학

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이 논문을 의학석사 학위논문으로 제출함

2021년 2월

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최경학의 의학석사학위 논문을 인준함

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Abstract

Research on long-term renal outcomes in acute kidney injury (AKI) patients with trauma, especially those with traumatic brain injury (TBI), has been limited. In this study, we compared the characteristics and management between stage 3 AKI patients with or without TBI who initiated renal replacement therapy (RRT) as per the Kidney Disease Improving Global Outcomes guideline, and analyzed whether TBI affects the disease progression.

Between 1 January 2014 and 30 June 2020, 51 patients who initiated RRT due to AKI after trauma were included. The patients were divided based on the presence or absence of TBI. The study endpoint was set to whether RRT persists at discharge and at the time of recent outpatient clinic.

Eight (15.6%) out of 51 patients required hemodialysis as per the most recent data. No significant within-group difference was found in terms of the baseline characteristics and management strategies. In the logistic regression analysis, TBI was independently associated with persistent RRT.

In conclusion, TBI is a risk factor for persistent RRT in patients with stage 3 AKI.

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기호 및 약어 설명

AIS = Abbreviated Injury Scale

AKI = Acute Kidney Injury

APACHE II = Acute Physiologic Assessment and Chronic Health Evaluation II

BUN = blood urea nitrogen

CAD = coronary artery disease

Cr = creatinine

CRP = C-reactive protein

CVA = cerebrovascular accident

DM = diabetes mellitus

GFR = glomerular filtration rate

HL = hyperlipidemia

HTN = hypertension

ICU = intensive care unit

ISS = injury severity score

PCT = procalcitonin

RRT = renal replacement therapy

TBI = traumatic brain injury

Introduction

Acute kidney injury (AKI) is one of the most common complications seen in critically ill patients. Acute renal failure was first described by William Heberden in 1802 [1]. Research on the current concepts of AKI had begun in earnest in 2004. The definition of AKI was coined by the Acute Dialysis Quality Initiative (ADQI) group based on the RIFLE criteria, which is a system for the diagnosis and classification of acute renal dysfunction [2]. This system consists of three grades of increasing severity (Risk, Injury, and Failure) and two classes of outcomes (Loss and End-stage renal disease). Several studies have reported that the RIFLE criteria are an independent predictor of outcome in critically ill patients with AKI [3−6]. A multicenter retrospective analysis using the RIFLE criteria in critically ill trauma patients also reported that AKI is independently associated with mortality [7]. Recently, the Acute Kidney Injury Network (AKIN), an international network of AKI researchers, endorsed the RIFLE criteria with a small modification. These modified criteria were validated by two recent studies [8, 9]. The Kidney Disease Improving Global Outcomes (KDIGO) group merged this new consensus definition based on the RIFLE criteria and the AKIN definition, which is now widely accepted [10].

Several studies have reported that the incidence of AKI in trauma patients varies from 1 to 50% [11-20]. This broad range is probably due to the heterogeneous AKI criteria used, the differences in the trauma severity, and the length of the follow-up period [21]. Trauma patients are highly exposed to conditions aggravating kidney injury, such as shock, ischemia, reperfusion, nephrotoxic agents, abdominal compartment syndrome, and direct kidney injury. In many studies, various causes for the development of AKI have been identified, including sepsis, critical illness, shock, burns, trauma, cardiac surgeries, major non-cardiac surgeries,

nephrotoxic drugs, radio-contrast agents, and poisons. The chance of developing AKI due to these factors differs among individuals based on their susceptibility. Among the causes of AKI, the proven risk factors of AKI in trauma patients include old age, hemorrhage, rhabdomyolysis, traumatic inflammation, and medical comorbidities [22, 23]. Trauma triggers these initial AKI risk factors and leads to impaired renal dysfunction caused by emergency operations, interventions, or systemic infections [24].

AKI is associated with prolonged intensive care unit length of stay and a significantly higher risk of mortality, which increases public health expenses [25]. As such, many studies have been conducted on AKI in severe trauma patients; however, a few studies have been conducted on long term outcomes, including disease progression to end-stage renal disease (ESRD).

Non-neurological organ dysfunction often accompanies traumatic brain injury (TBI), which leads to poor outcomes [26]. Several studies have reported the association between TBI and the development of AKI [27, 28]. Nongnuch et al. presented that acute brain injury affects the kidneys, leading to several changes in renal function, ranging from altered functions and electrolyte imbalances to inflammatory changes in brain death kidney donors [29]. Nonetheless, the effect of TBI-associated AKI on long-term renal outcomes has not been fully investigated. The association between TBI and renal disease progression to chronic kidney disease (CKD) or ESRD is still not well-known.

Wu et al. presented in a nationwide cohort study with 32,152 patients that TBI has a significant effect on incident CKD, but not on ESRD [30]. However, this study was not limited to critically ill patients, but included all TBI patients of mild cases. With the development of advanced patient transport systems, critical patients who once died in the field are now able to reach the trauma centers in time. In addition, intensive care medicine

has also evolved, and the preventable mortality rate has reduced. On the other hand, trauma centers can successfully treat more severe cases. Treatment goals for trauma patients have changed. Now, rather than simple survival, smooth rehabilitation to the general society and improved quality of life have become the goals of treatment. Furthermore, improving organ function is a priority. With this background, we compared the management between stage 3 AKI patients with or without TBI who initiated RRT as per the Kidney Disease Improving Global Outcomes (KDIGO) guideline, and analyzed whether TBI affects the disease progression.

Materials and Methods

Ethics

This retrospective observational study was based on data obtained from the registry of a single level 1 trauma center. The study protocol was approved by the Institutional Review Board of Ulsan University Hospital (2020-10-027), which waived the need for informed consent.

Study design and population

Between 1 January 2014 and 30 June 2020, 123 patients underwent RRT due to AKI after trauma, which correspond to stage 3 AKI according to KDIGO guideline (Table 1). To clarify the long-term outcomes of the enrolled patients, we excluded 48 patients who expired following the discontinuation of life-sustaining treatment within 24 hours. We also excluded 18 patients with a history of known chronic kidney disease, which might influence the outcome as confounding factors. Moreover, six patients whose initial diagnosis was not

related to trauma were excluded. Finally, 51 patients were enrolled in this study; TBI was identified in 20 patients, and in the remaining 31, the clinical conditions were not related to TBI. Figure 1 shows the study enrollment flow.

Definitions and study endpoints

RRT includes both continuous RRT (CRRT) and conventional hemodialysis (HD). We administered CRRT to all registered patients at the initiation of resuscitative treatment and then converted to HD after hemodynamic stability was achieved. The primary endpoint was RRT-free discharge. We examined whether to provide RRT at discharge and at the latest outpatient clinic follow-up point.

Statistical analyses

The categorical variables were represented as frequencies and percentages, and the continuous variables were reported as medians and ranges. The categorical variables were compared using the chi-squared test or Fisher's exact test (when the chi-squared test was not available). The continuous variables were compared using Student's *t*-test or the Mann-Whitney test (when the Student's *t*-test was not appropriate). Significant variables (p <0.25) in the univariate analysis were analyzed by logistic regression for their association with the disease progression. A p-value of <0.05 was considered statistically significant. All statistical analyses were performed using SPSS version 21.0 (IBM Corp., Armonk, NY, USA).

Results

Demographic characteristics of the patients

Of the 123 patients, 72 were excluded based on the criteria, and consequently, 51 were enrolled. The median age was 55 years and 76.5% of the patients were male. The median injury severity score (ISS) was 25 and the median Acute Physiologic Assessment and Chronic Health Evaluation II (APACHE II) score was 26. A total of 39.2% of patients had TBI, 33.3% had hypertension, and 7.8% had diabetes. Forty-six patients required emergency surgeries on multiple sites, and 8 out of 51 patients underwent RRT at discharge as the disease progressed. The median number of follow-up days was 489. The baseline characteristics of the patients are shown in Table 2.

Comparison of the patients depending on the presence of TBI

We divided the patients into two groups according to the presence of TBI, and the groups were compared (Table 3). There was no significant difference in the baseline characteristics between the two groups, including age, gender, and premedical history. There was no significant difference in terms of ISS and APACHE II scores. In addition, we compared the worst values of clinically-related laboratory data from admission to during RRT. The laboratory values reflecting renal function and the inflammatory response showed no differences. Both groups were administered with vasopressors to a similar extent. The serum lactate level was higher in the TBI group; however, the difference was not significant. Two patients in the non-TBI group required RRT and 6 in the TBI group were undergoing RRT at discharge and at the latest outpatient clinic follow-up point, which showed a significant difference (p <0.05).

Risk factors of persistent RRT

Significant variables (p <0.25) in the univariate analysis were analyzed by logistic regression for their association with persistent RRT. Factors known to affect renal functions and thought to be clinically relevant were also included in the analysis. Table 4 shows that TBI was independently associated with persistent RRT with more than 9 times increase in odds ratio, while the other variables did not reach statistical significance. After confirming that TBI is a risk factor, we conducted a comparative analysis of the entire TBI group depending on the status of persistent RRT to figure out the factors that make the differences in outcome. Although it was difficult to appreciate statistically significant results due to the small number of patients, the two groups showed differences only in the indicators of renal function, and there was no difference in the other variables including the severity of head trauma (Table 5). The use of hydroxyethyl starch and diuretics, commonly known to cause renal dysfunction, was not found in both groups (data not shown).

Discussion

Patients with kidney diseases have a lower health-related quality of life (QOL), with approximately a 7% reduction for stage 4 or 5, as compared to the general population of the same age. Kidney diseases might affect health-related QOL in several ways. First, just the diagnosis of kidney diseases alone can cause fear, anxiety, and depression. Second, symptoms of co-existing comorbidities also negatively affect daily life. Some patients with ESRD report their health-related QOL similar to that of those with terminal malignancies. Third, the prevention, diagnosis, and treatment-related costs are considered cost-effective at 50,000 USD per QALY. Fourth, the five-year survival rate of patients with ESRD on dialysis is up to

60% lower as compared to that of the general population of the same age [31].

AKI to CKD transition is mainly caused by maladaptive repair of kidney injury. This process includes many pathophysiological processes, e.g., cell death or acute tubular necrosis, renal fibrosis, etc. which are characterized by the accumulation of extra cellular matrix (ECM), capillary rarefaction by endothelial to mesenchymal transition, tubular epithelial cell senescence, and consequently inflammatory processes [32]. Therefore, the treatment of AKI aims to maintain urine volume and avoid the development of hypotension by fluid resuscitation, preferably with balanced crystalloid and managing electrolyte imbalance, acid-base disturbance**,** and nutrition.

Recent studies have stated that the incidence rate of AKI in TBI patients is up to 20% [28, 33]. Overall the prevalence of AKI in trauma patients has been reported to be up to 20.4% [25]; hence, it is possible to assume that the degree of kidney injury is initially similar in patients with or without TBI. Chia-Lin et al. [30] performed a retrospective observational analysis of long-term renal outcomes of TBI patients and found that patients with TBI developed significantly more CKD than those without; however, there was no difference in the progression to ESRD. Federica et al. [33] carried out an *in vitro* study with human tubular epithelial cells to clarify the association between severe TBI and acute tubular injury. Although the mechanism of kidney injury in TBI patients have not been fully elucidated, this study showed that the inflammatory process associated with TBI correlates with renal function. TBI triggers a complex cascade of cellular events, leading to systemic inflammation and kidney and other organ damage. Furthermore, circulating inflammatory cytokines and chemokines might be responsible for disease progression toward chronic kidney disease. A series of the processes is also observed in severe sepsis, which is initiated with microvascular coagulopathy, followed by dysregulation of cellular carrier expression and mitochondrial

dysfunction in tubular epithelial cells and, finally, apoptosis. Based on this feature, further research can be conducted in microvascular level. Federica et al. also mentioned that this hypothesis might be supported by the increased neutrophil gelatinase-associated lipocalin (NGAL) level, which was significantly elevated, even if biomarkers currently used for the diagnosis of AKI appeared to be within the normal range.

Based on many studies that looked into the relationship between TBI and renal function, we compared and analyzed the enrolled patients according to whether or not they had TBI. We found that TBI patients required persistent RRT at discharge and at the latest outpatient clinic points, which was significantly more than in those without TBI. In this study, eight trauma patients required RRT, and the sole risk factor of persistent RRT due to disease progression was TBI. All variables appeared to have no significant difference among patients with or without TBI. Also, the two groups showed no difference in the APACHE II and ISS scores, implying that the injuries were of the same magnitude [34]. In order to find the cause of the significant difference in the results, we further investigated the treatment strategies of the patients group, but none of the variables showed a significant difference, including fluid and nephrotoxic drug usage, which was observed only in a single patient on persistent RRT group. A considerable limitation of this study is the heterogeneity in the management; patients with TBI were managed mainly by neurosurgeons and those without TBI were managed by general surgeons. Therefore, consistent treatments was not applied to the patients to be studied. In addition, this study was a retrospective analysis conducted with a single trauma center registry data of a relatively small number of patients in each group. Selection and information biases might have affected the results. Moreover, the diagnosis of AKI and initiation of RRT were based on patients' clinical status judged by diverse physicians. It was also a limitation of this study that long-term follow-up of the patients was not performed, we

were unable to determine whether the renal function of the study subjects was recovered or worsened.

Conclusion

Traumatic brain injury is a risk factor for persistent renal replacement therapy in trauma patients who develop stage 3 AKI. Moreover, kidney disease can progress without manifesting signs, and thus, the diagnosis of CKD can be missed if the physicians monitor only currently used biomarkers of renal function. Thus, physicians should be aware of renal protection in managing TBI patients.

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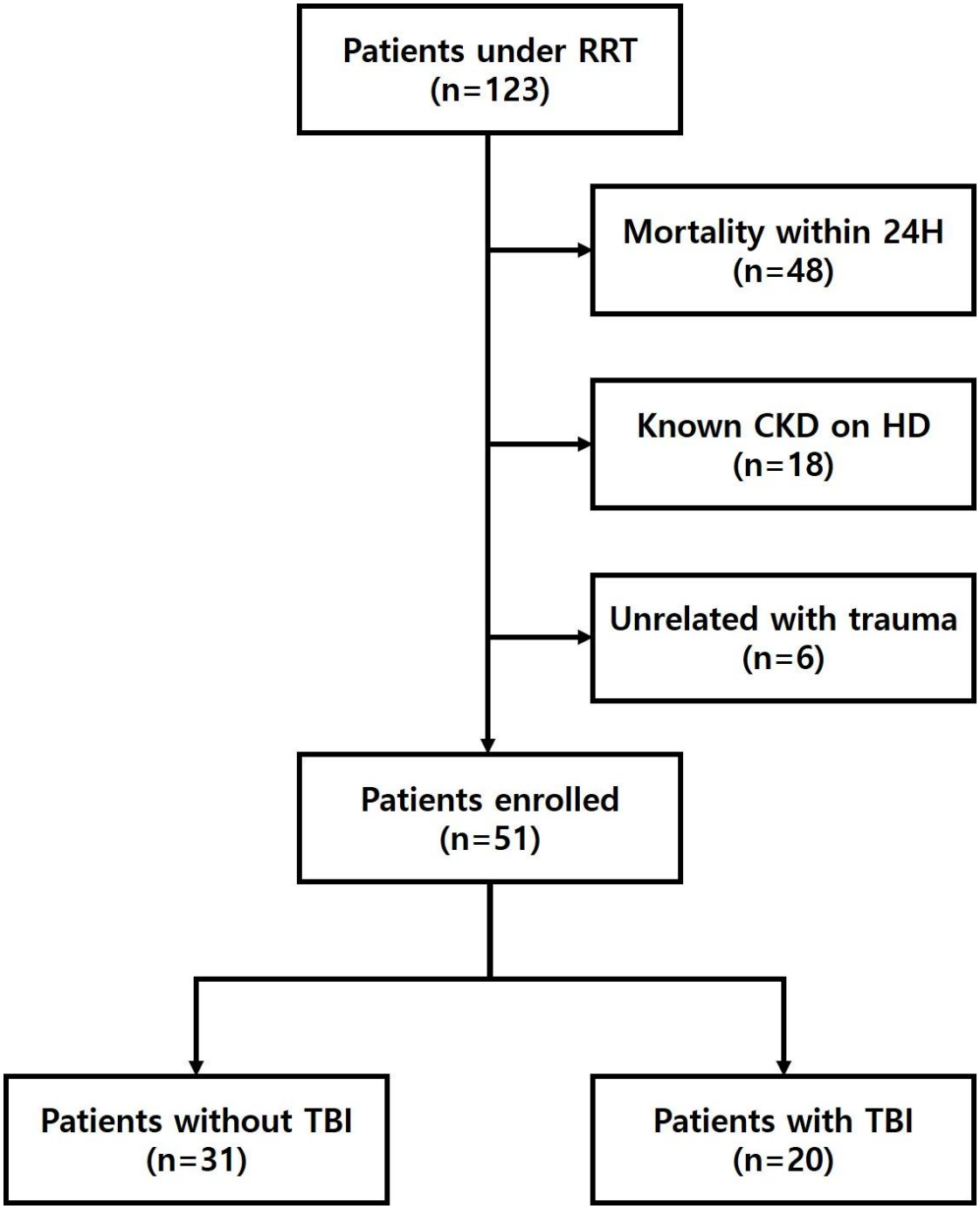

Figure 1. Study enrollment flow.

Table 1. Staging of AKI According to KDIGO

Stage	Serum Creatinine	Urine Output
1	1.5-1.9 times baseline or ≥0.3 mg/dL (≥26.5 μmol/L) increase	<0.5 mL/kg/h for 6-12 h
2	2.0-2.9 times baseline	<0.5 mL/kg/h for ≥12 h
3	3.0 times baseline or Increase in sCr to ≥4.0mg/dL (≥353.6 μmol/L) or Initiation of renal replacement therapy	<0.3 mL/kg/h for ≥24 h or Anuria for ≥12 h

Table 2. General characteristics of the patients.

Characteristic		
Age, median (range)	55	(18−84)
Male, n (%)	39	(76.5%)
ISS, median (range)	25	(4−50)
APACHE II, median (range)	26	(4−41)
TBI, median (range)	20	(39.2%)
HTN, n (%)	17	(33.3%)
DM, n (%)	4	(7.8%)
HL, n (%)	2	(3.9%)
CVA, n (%)	3	(5.9%)
CAD, n (%)	4	(7.8%)
Malignancy, n (%)	3	(5.9%)
Operation, n (%)	46	(90.2%)
Head and neck, n	16	
Thorax, n	8	
Abdominopelvic, n	29	
Spine, n	2	
Extremities, n	24	
RRT at discharge, n (%)	8	(15.7%)
Follow up days, median (range)	489	(15−2348)

ISS, injury severity score; APACHE II, Acute Physiologic Assessment and Chronic Health Evaluation II; TBI, traumatic brain injury; HL, hyperlipidemia; CVA, cerebrovascular accident; CAD, coronary artery disease; RRT, renal replacement therapy.

Table 3. Comparison of patient groups according to TBI.

Variables	**Non TBI (n=31)**		**TBI (n=20)**		***p*-value**
Age, median (range)	58	(18−84)	54	(18−77)	0.699
Male, n (%)	24	(77.4%)	15	(75%)	-
ISS, median (range)	22	(5−43)	29	(4−50)	0.119
APACHE II, median (range)	27	(5−41)	26	(4−35)	0.595
HTN, n (%)	10	(32.3%)	7	(35%)	0.839
DM, n (%)	1	(3.2%)	3	(15%)	0.287
HL, n (%)	1	(3.2%)	1	(5%)	-
CVA, n (%)	1	(3.2%)	2	(10%)	0.553
CAD, n (%)	2	(6.5%)	2	(10%)	0.640
Malignancy, n (%)	1	(3.2%)	2	(10%)	0.553
Vasopressor, n (%)	28	(90.3%)	18	(90%)	-
Lactate (mmol/l), median (range)	4.80	(1.00−14.00)	6.05	(0.90−15.00)	0.429
CRP (mg/l), median (range)	26.19	(4.37−46.22)	29.235	(5.19−43.05)	0.385
PCT (ng/ml), median (range)	8.38	(0.33−154.99)	6	(0.42−403.90)	0.805
BUN (mg/dl), median (range)	85.6	(25.60−183.30)	83.9	(23.90−159.90)	0.938
Cr (mg/dl), median (range)	5	(1.38−11.75)	4.62	(1.19−13.11)	0.602
GFR (ml/min/1.73 m^2), median (range)	12	(1.00−57.00)	14.5	(4.00−53.00)	0.595
ICU days, median (range)	34	(4−131)	37.5	(3−253)	0.582
RRT at discharge, n (%)	2	(6.5%)	6	(30%)	0.045

ISS, injury severity score; APACHE II, Acute Physiologic Assessment and Chronic Health Evaluation

II; HTN, hypertension; DM, diabetes mellitus; TBI, traumatic brain injury; HL, hyperlipidemia; CVA, cerebrovascular accident; CAD, coronary artery disease; RRT, renal replacement therapy; CRP, C-reactive protein; PCT, procalcitonin; BUN, blood urea nitrogen; Cr, creatinine; GFR, glomerular filtration rate; ICU, intensive care unit.

Table 4. Logistic regression analysis of risk factors for persistent RRT.

Variable	Univariate analysis		Multivariate analysis	
	OR (95% CI)	***p*-value**	**OR (95% CI)**	***p*-value**
Age	1.027 (0.982−1.075)	0.248	1.031 (0.968−1.097)	0.344
Male	0.909 (0.158−5.230)	0.915		
ISS	1.023 (0.958−1.093)	0.490	1.022 (0.945−1.105)	0.592
TBI	6.214 (1.110−34.799)	0.038	9.486 (1.101−81.742)	0.041
HTN	2.308 (0.499−10.669)	0.284	0.582 (0.043−7.838)	0.684

ISS, injury severity score; HTN, hypertension; TBI, traumatic brain injury.

Table 5. Comparison of TBI patients according to the status of persistent RRT.

Variables	**Non-RRT (n=14)**		**RRT (n=6)**		***p*-value**
Age, median (range)	53.5	(18−76)	64.5	(33−77)	0.173
Male, n (%)	11	(78.6%)	4	(66.7%)	0.613
ISS, median (range)	29.5	(4−50)	19.5	(9−43)	0.456
APACHE II, median (range)	26	(6−35)	24	(4−29)	0.231
AIS, Head, median	3.5	(2-5)	4	(3-5)	0.391
HTN, n (%)	4	(28.6%)	3	(50.0%)	0.613
DM, n (%)	3	(21.4%)	0	(0.0%)	0.521
HL, n (%)	1	(7.1%)	0	(0.0%)	−
CVA, n (%)	2	(14.3%)	0	(0.0%)	−
CAD, n (%)	2	(14.3%)	0	(0.0%)	−
Malignancy, n (%)	0	(0.0%)	2	(33.3%)	0.079
Operation, n (%)	13	(92.9%)	5	(83.3%)	0.521
Vasopressor, n (%)	12	(85.7%)	6	(100.0%)	−
Lactate (mmol/l), median (range)	6.45	(0.9−15.0)	3.80	(2.06−8.20)	0.302
CRP (mg/l), median (range)	27.36	(5.19−39.57)	35.06	(25.78−43.05)	0.013
PCT (ng/ml), median (range)	6.00	(0.42−55.80)	7.96	(0.89−403.90)	0.888
BUN (mg/dl), median (range)	66.9	(23.9−159.9)	109.3	(60.2−154.9)	0.248
Cr (mg/dl), median (range)	3.62	(1.19−8.54)	6.33	(4.46−13.11)	0.058
GFR (ml/min/1.73 m^2),	17.5	(8−53)	7.5	(4−29)	0.002

median (range)					
ICU days, median (range)	37.5	(3−253)	32	(15−69)	0.620
RRT at discharge, n (%)	8.5	(1−23)	18	(9−38)	0.082

ISS, injury severity score; APACHE II, Acute Physiologic Assessment and Chronic Health Evaluation II; AIS, Abbreviated Injury Scale; HTN, hypertension; DM, diabetes mellitus; TBI, traumatic brain injury; HL, hyperlipidemia; CVA, cerebrovascular accident; CAD, coronary artery disease; RRT, renal replacement therapy; CRP, C-reactive protein; PCT, procalcitonin; BUN, blood urea nitrogen; Cr, creatinine; GFR, glomerular filtration rate; ICU, intensive care unit.

국문 요약

외상성 급성 신장 손상 환자, 특히 외상성 뇌 손상 환자의 장기적인 신장 기능에 대한 연구는 제한되어 있다. 이 연구는, 외상 후 신대치요법을 시작한, KDIGO 가이드라인 3단계에 해당하는 급성 신부전 발생 환자를 외상성 뇌 손상 유무로 나누어, 각 집단의 환자 특성과 치료 방법을 비교하였고, 외상성 뇌 손상이 급성 신부전 질환의 진행에 영향을 미치는지 분석하였다.

2014 년 1 월 1 일부터 2020 년 6 월 30 일까지, 외상 수상 후 발생한 급성 신부전으로 신대치요법을 시작한 51 명이 포함되었으며, 환자들은 외상성 뇌 손상의 유무에 따라 나뉘었다. 퇴원 시점 및 가장 최근의 외래 진료 방문 시점에서 신대치요법을 지속하고 있는지 여부를 조사하여 두 집단을 비교 분석하였다.

가장 최근 시점까지, 총 51명의 환자 중에서 8명이 혈액 투석 치료를 지속하고 있었다. 두 그룹의 환자 사이에 기본적인 특성과 치료 방침에 유의미한 차이는 발견되지 않았다. 로지스틱 회귀 분석 결과 외상성 뇌 손상은 지속적인 신대치요법 적용과 관련이 있는 것으로 밝혀졌다.

결론적으로, 외상성 뇌 손상은 3 단계의 급성 신부전 환자에서 지속적인 신대치요법 적용의 위험 인자이다.