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Evaluation of diagnostic biomarkers for acute kidney injury in major burn patients

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Purpose: Acute kidney injury (AKI) in major burn patients is a common complication with high morbidity and mortality. The mainstream treatment is early diagnosis and rapid termination and prevention of the underlying insult. Therefore, it's essential to identify early biomarkers predicting AKI.
Methods: A total of 85 patients who were admitted to the burn intensive care unit from June 2012 to July 2013 were included in this prospective cohort study. Ten biomarkers (blood urea nitrogen, serum creatinine, urine creatinine, cystatin C, cystatin C glomerular filtration rate, AST, lacate dehydrogenase [LD], creatine kinase, lactic acid, and myoglobin) were obtained at time of admission and evaluated as diagnostic biomarkers to predicting AKI and early AKI.
Results: Out of 85 patients, 35 patients were dead and overall mortality was 41.2%. The mean age was 49.4 years and mean percentage of total body surface area was 53.2%. Area under the curve (AUC) of receiver operating characteristic curve of biomarkers on predicting AKI were 0.746, 0.718, and 0.717 in LD, lactic acid, and serum creatinine, respectively. AUC of cystatin C predicting AKI was much lower at 0.555. AUC of biomarkers on predicting early AKI were 0.833, 0.816, 0.790, and 0.759 in LD, serum creatinine, AST, and serum myoglobin.
Conclusion: LD, lactic acid and serum creatinine were acceptable as diagnostic biomarkers of AKI and LD, serum creatinine, AST, and serum myoglobin were reasonable as diagnostic biomarkers of early AKI. However, cystatin C was an unfavorable biomarker in major burn patients.
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Key Words: Acute kidney injury, Biological biomarker, Burns, Cystatin C, Lactate dehydrogenase

INTRODUCTION

Acute kidney injury (AKI) is a common complication in burn patients as well as critically ill patients with incidences reported ranging from 1% to 40%, and mortality reported ranging from 50% to 100% [1-4]. The mortality associated with AKI remains exceedingly high in these patients despite advances of critical care and renal replacement therapy (RRT). The incidence of AKI patients who need RRT has been up to 50% in burned patients [2]. Because severe burn is typically characterized by stress, inflammation, and hypermetabolism and is one of the most severe forms of acute trauma, it's still difficult to cope with and predict critical changes such as renal, cardiovascular and hepatic dysfunctions. The adequate treatment of AKI is early diagnosis and rapid termination and prevention of the underlying insult while preserving kidney function [5]. Although known risk factors are generally old age, total body surface area (TBSA) burned, sepsis and multiorgan dysfunctions in burned patients with AKI [6-8], many studies have been conducted to identify early biomarkers to diagnose AKI in critically ill patients.

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Most studies have reviewed blood urea nitrogen (BUN) and serum creatinine as routinely available clinical biomarkers of glomerular filtration and severity of kidney injury. However, BUN and serum creatinine have had some serious limitations in practice to provide either a sensitive or specific indication of the development of AKI and renal function and these limitations were as follows: (1) nonrenal events such as urea overproduction in hypercatabolic states and excess creatinine generation with rhabdomyolysis can independently influence BUN and creatinine levels, (2) there is minimal or no change of creatinine levels in significant renal disease due to renal reserve, enhanced tubular secretion of creatinine, (3) BUN and creatinine levels are no longer alongside with the severity of AKI due to fixed rates of BUN and creatinine generation [9-11]. Recently, several favorable biomarker candidates such as urinary kidney injury molecule-1, neutrophil gelatinase-associated lipocalin, interleukin-18, cystatin C, clusterin, fatty acid binding protein-liver type and osteopontin have not only emerged [10,11], but also other biomarkers such as creatine kinase (CK), AST, lactate dehydrogenase (LD), serum and urine myoglobin have still been described and showed variable results [9,12-15].

The aim of this study was to evaluate accuracy and reliability of the biomarkers for the diagnosis of AKI and for the early prediction of the development of AKI in major burn patients.

METHODS

Patient selection

This prospective cohort study included 85 consecutive patients who were admitted to the burn intensive care unit (BICU) at Burn Center, Hangang Sacred Heart Hospital, Hallym University from June 2012 to July 2013. All patients were over the age of 18 with over 20% TBSA burned and were admitted to our BICU within 6 hours after injury because we intended to investigate early biomarkers predicting AKI in major burn patients. As exclusion criteria, we did not enroll patients with known cardiac disease (prior history of heart failure, arrhythmia and coronary heart disease etc.), prior kidney transplant, end-stage kidney disease and chronic liver disease (prior history of liver cirrhosis and chronic hepatitis etc.) to exclude the influence of other organs.

Variables predicting and early AKI and definition of AKI

Variables were collected for each patient including age, sex, percentage of TBSA burned, percentage of TBSA third degree burn wound, cause of burn injury, and presence of inhalation injury for all patients. The Abbreviated Burn Severity Index (ABSI) score [16] is calculated by assigning a numerical value to the age, sex, extent of burns, presence of full-thickness burns and presence of inhalation injury depending on their severity, and then adding all five values, and the Sequential Organ Failure Assessment (SOFA) score [17] is calculated by assigning a point value from 0 (normal) to 4 (high degree of organ dysfunction) to 6 variables, each representing and organ failure were used for severity of illness score for hospital mortality.

We divided into AKI and non-AKI groups to evaluate early biomarkers predicting AKI. Then, we further divided into early and late AKI groups among AKI groups to review differences between the two groups because early AKI occurs during the first 5 days after injury and late AKI begins more than 5 days after injury [2]. Ten biomarkers such as BUN, serum creatinine, urine creatinine, cystatin C, cystatin C GFR (estimated glomerular filtration rate by cystatin C), AST, LD, CK, lactic acid and myoglobin were obtained at time of admission and evaluated as predicting factors.

Diagnosis of AKI was made by RIFLE (Risk, Injury, Failure, Loss of kidney function, and End-stage disease) criteria [18]. Patients who met any of the criteria of the RIFLE classification were defined as AKI patients, in case of increase in serum creatinine of at least 50% from baseline or a reduction in urine output to <0.5 mL/kg/hr for >6 hours. Baseline renal function is defined as the lowest known serum creatinine value during the preceding 3 months. For patients without known prior serum creatinine, we used lowest serum creatinine levels during the admission period when it was only within normal range. But the lowest serum creatinine was still abnormal in 5 patients. In this case, the baseline serum creatinine was estimated using a modification of diet in renal disease equation for assessment of kidney function, assuming a GFR of 75 mL/min per 1.73 m^2 [18]. This study was approved by the Institutional Review Board of Hangang Sacred Heart Hospital (IRB No. 2012-045) and informed consents were obtained from lineal family members of the patients.

Data analysis

Statistical analyses were conducted using SPSS ver. 17.0 (SPSS Inc., Chicago, IL, USA). All continuous variables were presented as mean ± standard deviation, and the frequencies of categorical variables were presented as percentages. Continuous variables were analyzed with the independent t-test when there were normal distributions and with Mann-Whitney U-test when there were no normal distributions. Categorical variables were analyzed with the chi-square test. Diagnostic characteristics of all ten biomarkers (BUN, serum creatinine, urine creatinine, cystatin C, cystatin C GFR, AST, LD, CK, lactic acid, serum myoglobin) predicting overall AKI and early AKI were assessed by receiver operating characteristic (ROC) curve analysis. The areas under the curve (AUC) of the ROC plots range from 1.0 (perfect separation of test values into two groups) to 0.5 (no distributional difference). An AUC > 0.7 indicates a discriminating strength of statistical significances; an AUC > 0.8

indicates excellent discriminating power for the test [19]. Cutoff value of each biomarker was defined by Youden's index. Uni- and multivariate logistic regression analysis was performed to evaluate individual predictive power of biomarkers for detecting overall AKI and early AKI. A P-value under 0.05 is considered statistically significant.

RESULTS

Patient demographics and comparisons between AKI and non-AKI groups

Out of 85 patients, 35 patients were dead and overall mortality was 41.2%, and mortality rates were significantly higher (64.4%, 31 out of 48) in AKI group. The mean age of all patients was 49.4 ± 15.0 years. A male preponderance was noted in this study. The presence of inhalation, percentage of TBSA burned, percentage of full-thickness burned, ABSI score, SOFA score, length of stay and mortality showed significant differences between the two groups ($P < 0.05$) (Table 1). Serum creatinine (0.93 *vs.* 0.71), AST (169.9 *vs.* 90.6), LD (766.0 *vs.* 452.4), lactic acid (5.15 *vs.* 3.00), and serum myoglobin (491.5 *vs.* 287.0) were significantly greater in AKI group and cystatin C (0.79 *vs.* 0.70) was higher in AKI group, but showed no significant difference (Table 1).

Patient demographics and comparisons between early and late AKI groups

The prevalence of AKI was 56.5% (48 out of 85) among those admitted to our BICU with a mortality rate of 64.6%. Out of 48 patients with AKI, patients with early AKI were 25 and late were 23. All demographic variables (age, sex, causes, presence of inhalation, TBSA burned, full-thickness burned) and two scoring systems of severity (ABSI score and SOFA score) and mortality showed no significant differences and interval of AKI, number of CRRT application and length of stay showed significant differences (Table 2). The levels of biomarkers such as serum creatinine, cystatin C, cystatin C GFR, AST, LD, CK, serum myoglobin, and presence of myoglobinuria showed significant differences between early and late AKI groups.

Comparison of each biomarker on diagnosis of AKI and early AKI

In diagnosis of overall AKI, the statistical significant cutoff values of LD, lactic acid, serum creatinine, AST, and serum myo-

Table 1. Patient demographics and comparisons between AKI and non-AKI group

Variable	Total (n = 85)	AKI (n = 48)	Non-AKI (n = 37)	P-value
Age (yr)	49.4 ± 15.0	51.9 ± 14.5	46.2 ± 15.2	0.086
Sex, male:female	72:13	42:6	30:7	0.546
FB:SB:EB:ChB:CoB	73:2:7:1:2	43:1:3:0:1	30:1:4:1:1	0.830
No. of inhalation	25 (29.4)	21 (43.8)	4 (10.8)	0.001
%TBSA burned	53.2 ± 21.2	63.1 ± 19.4	40.3 ± 16.1	<0.001
Full-thickness %	40.8 ± 23.5	51.31 ± 23.7	27.1 ± 14.6	<0.001
ABSI score	10.09 ± 2.54	11.29 ± 2.33	8.54 ± 1.89	<0.001
SOFA score	9.47 ± 4.38	7.51 ± 3.15	10.98 ± 4.62	<0.001
Interval of AKI	9.8 ± 12.4	9.8 ± 12.4	-	-
No. of CRRT application	22 (25.9)	22 (45.8)	-	-
LOS (day)	44.5 ± 35.0	37.9 ± 40.0	53.1 ± 25.1	0.035
Mortality	35 (41.2)	31 (64.6)	4 (10.8)	<0.001
BUN (mg/dL)	15.42 ± 4.70	15.82 ± 5.32	14.91 ± 3.79	0.523
Serum creatinine (mg/dL)	0.84 ± 0.29	0.93 ± 0.33	0.71 ± 0.17	0.001
Urine creatinine (mg/dL)	92.3 ± 59.1	87.0 ± 59.5	99.1 ± 58.8	0.481
Cystatin C (mg/L)	0.75 ± 0.25	0.79 ± 0.29	0.70 ± 0.18	0.386
Cystatin C GFR	116.4 ± 33.5	110.5 ± 29.2	124.0 ± 37.3	0.294
AST (IU/L)	135.4 ± 340.6	169.9 ± 420.5	90.6 ± 190.4	0.003
LD (IU/L)	629.5 ± 576.4	766.0 ± 702.0	452.4 ± 273.5	<0.001
CK (IU/L)	5,327.4 ± 31,339.7	6,971.3 ± 40,360.2	3,194.7 ± 12,521.5	0.354
Latic acid (mmol/L)	4.22 ± 3.25	5.15 ± 3.70	3.00 ± 2.01	0.001
Serum myoglobin (ng/mL)	402.5 ± 398.5	491.5 ± 406.2	287.0 ± 361.8	0.012
Myoglobinuria	28 (32.9)	20 (41.7)	8 (21.6)	0.064

Values are presented as mean ± standard deviation or number (%).
AKI, acute kidney injury; FB, flame burn; SB, scald burn; EB, electrical burn; ChB, chemical burn; CoB, contact burn; %TBSA burned, percentage of total body surface area burned; ABSI, Abbreviated Burn Severity Index; SOFA, Sequential Organ Failure Assessment; AKI, acute kidney injury; CRRT, continuous renal replacement therapy; LOS, length of hospital stay; GFR, glomerular filtration rate; LD, lactate dehydrogenase; CK, creatine kinase.

Table 2. Patient demographics and comparisons between early AKI and late AKI group

Variable	AKI (n = 48)	Early (n = 25)	Late (n = 23)	P-value
Age (yr)	51.9 ± 14.5	51.0 ± 16.2	52.8 ± 12.7	0.660
Sex, male:female	42:6	22:3	20:3	>0.999
FB:SB:EB:ChB:CoB	43:1:3:0:1	23:0:2:0:0	20:1:1:0:1	0.457
No. of inhalation	21 (43.8)	13 (52.0)	8 (34.8)	0.259
%TBSA burned	63.1 ± 19.4	65.4 ± 19.9	60.6 ± 19.0	0.398
Full-thickness %	51.31 ± 23.7	55.2 ± 26.0	47.1 ± 20.7	0.246
ABSI score	11.29 ± 2.33	11.64 ± 2.53	10.91 ± 2.09	0.286
SOFA score	10.68 ± 4.62	10.20 ± 5.44	11.82 ± 3.4	0.227
Interval of AKI	9.8 ± 12.4	1.24 ± 0.66	19.13 ± 12.34	<0.001
No. of CRRT application	22 (45.8)	7 (28.0)	15 (65.2)	0.019
LOS (day)	37.9 ± 40.0	32.4 ± 46.9	43.9 ± 30.7	0.013
Mortality	31 (64.6)	18 (72.0)	13 (56.5)	0.367
BUN (mg/dL)	15.82 ± 5.32	16.64 ± 6.14	14.93 ± 4.19	0.269
Serum creatinine (mg/dL)	0.93 ± 0.33	1.08 ± 0.37	0.77 ± 0.16	0.001
Urine creatinine (mg/dL)	87.0 ± 59.5	79.7 ± 60.3	94.8 ± 59.0	0.364
Cystatin C (mg/L)	0.79 ± 0.29	0.90 ± 0.31	0.68 ± 0.21	0.004
Cystatin C GFR	110.5 ± 29.2	100.0 ± 30.5	121.9 ± 23.5	0.007
AST (IU/L)	169.9 ± 420.5	268.6 ± 568.7	62.6 ± 41.6	0.001
LD (IU/L)	766.0 ± 702.0	1050.1 ± 885.1	457.3 ± 82.4	<0.001
CK (IU/L)	6,971.3 ± 40360.2	12,928.2 ± 55,786.1	496.5 ± 921.5	0.015
Latic acid (mmol/L)	5.15 ± 3.70	6.34 ± 4.68	3.86 ± 1.45	0.103
Serum myoglobin (ng/mL)	491.5 ± 406.2	670.6 ± 376.2	296.8 ± 349.4	0.002
Myoglobinuria	20 (41.7)	17 (68.0)	3 (13.0)	<0.001

Values are presented as mean ± standard deviation or number (%).
AKI, acute kidney injury; FB, flame burn; SB, scald burn; EB, electrical burn; ChB, chemical burn; CoB, contact burn; %TBSA burned, percentage of total body surface area burned; ABSI, Abbreviated Burn Severity Index; SOFA, Sequential Organ Failure Assessment; AKI, acute kidney injury; CRRT, continuous renal replacement therapy; LOS, length of hospital stay; GFR, glomerular filtration rate; LD, lactate dehydrogenase; CK, creatine kinase.

Table 3. Area under the curve (AUC) of receiver operating characteristic curve of biomarkers on prediction AKI

Variable	AUC predicting AKI (n = 48)				AUC prediction early AKI[a] (n = 25)				AUC predicting late AKI[b] (n = 23)			
	AUC	SE	Sig.	95% CI	AUC	SE	Sig.	95% CI	AUC	SE	Sig.	95% CI
LD	0.746	0.054	0.000	0.641–0.851	0.833	0.054	0.000	0.726–0.939	0.456	0.061	0.536	0.337–0.576
Lactic acid	0.718	0.056	0.001	0.608–0.829	0.701	0.070	0.004	0.564–0.837	0.561	0.062	0.392	0.440–0.681
Serum creatinine	0.717	0.055	0.001	0.610–0.824	0.816	0.054	0.000	0.711–0.922	0.438	0.065	0.381	0.311–0.565
AST	0.690	0.060	0.003	0.573–0.807	0.790	0.052	0.000	0.689–0.892	0.431	0.064	0.332	0.307–0.556
Serum myoglobin	0.657	0.060	0.013	0.539–0.776	0.759	0.059	0.000	0.643–0.874	0.424	0.066	0.283	0.294–0.554
CK	0.559	0.063	0.354	0.434–0.683	0.674	0.065	0.012	0.546–0.802	0.390	0.065	0.122	0.262–0.519
Cystatin C	0.555	0.063	0.387	0.431–0.679	0.701	0.064	0.004	0.576–0.826	0.357	0.063	0.143	0.232–0.481
BUN	0.541	0.063	0.523	0.418–0.663	0.569	0.075	0.318	0.421–0.717	0.478	0.069	0.755	0.342–0.614
Urine creatinine	0.455	0.063	0.481	0.331–0.580	0.414	0.072	0.213	0.273–0.555	0.535	0.069	0.624	0.400–0.669
Cystatin C GFR	0.434	0.063	0.296	0.310–0.557	0.305	0.065	0.005	0.177–0.432	0.623	0.064	0.083	0.498–0.747

AKI, acute kidney injury; SE, standard error; Sig, significance (P-value); CI, confidence interval; LD, lactate dehydrogenase; CK, creatine kinase; GFR, glomerular filtration rate.
[a]Early AKI, AKI developed within 5 days after injury. [b]Late AKI, AKI developed after 5 days from injury.

globin were 450 IU/L, 3.0 mmol/L, 0.8 mg/dL, 50 IU/L and 170 ng/dL, respectively. LD had the greatest AUC (0.746, $P < 0.001$) (Table 3). In diagnosis of early AKI, the statistical significant cutoff values of LD, serum creatinine, AST, serum myoglobin, lactic acid, and cystatin C were 480 IU/L, 0.85 mg/dL, 60 IU/L, 270 ng/dL, 3.7 mmol/L and 0.72 mg/L, respectively. LD and serum creatinine had AUC over 0.800 with $P < 0.001$ (Table 3). There were no significant biomarkers predicting late AKI (Table 3). Fig. 1 shows ROC curve on diagnosis of AKI and early AKI.

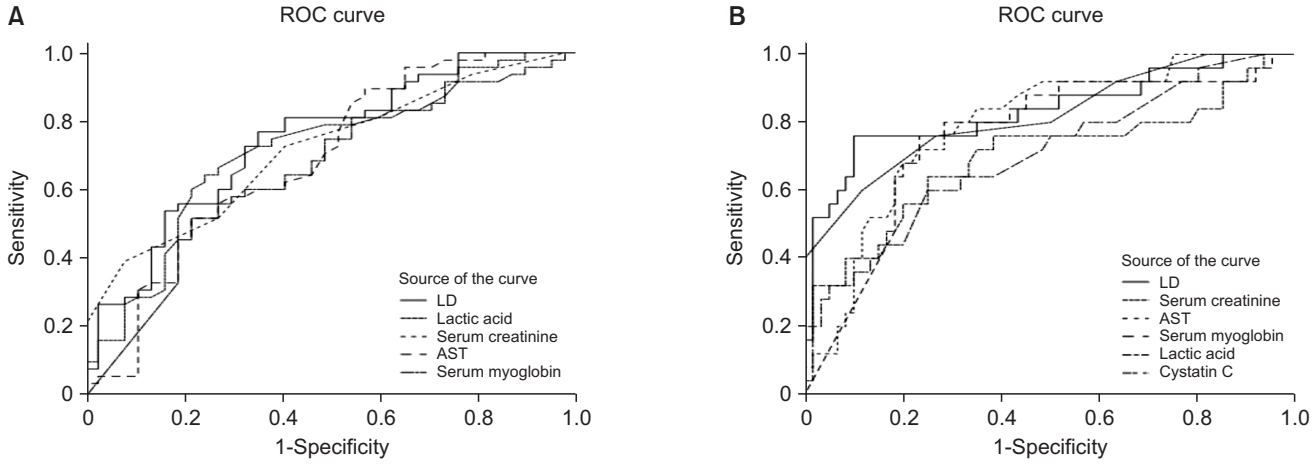

Fig. 1. The receiver operating characteristic (ROC) curves. (A) Lactate dehydrogenase (LD), lactic acid, serum creatinine, AST and serum myoblogin on diagnosis of overall acute kidney injury (AKI). (B) LD, serum creatinine, AST, serum myoglobin, lactic acid and cystatin C on diagnosis of early AKI.

Table 4. Univariate logistic regression

Variable	For predicting AKI in burn patients						For predicting early AKI in burn patients					
	B	SE	Wald	Sig.	Exp(B)	95% CI for Exp(B)	B	SE	Wald	Sig.	Exp(B)	95% CI for Exp(B)
LD	1.621	0.473	11.725	0.001	5.060	2.000–12.798	1.846	0.542	11.577	0.001	6.333	2.187–18.340
Lactic acid	1.468	0.472	8.546	0.001	4.879	1.898–12.956	1.564	0.521	8.998	0.003	4.776	1.719–13.264
Serum creatinine	1.077	0.470	5.257	0.022	2.935	1.169–7.367	2.164	0.552	15.382	0.000	8.708	2.953–25.684
AST	0.806	0.446	3.259	0.071	2.239	0.933–5.369	1.872	0.530	12.500	0.000	6.504	2.303–18.366
Serum myoglobin	0.894	0.448	3.974	0.046	2.444	1.015–5.886	2.251	0.555	16.446	0.000	9.500	3.200–28.201
Cystatin C	-	-	-	-	-	-	1.122	0.495	5.129	0.024	3.071	1.163–8.108

AKI, acute kidney injury; B, b coefficient; SE, standard error; Sig, significance (P-value); Exp(B), Exponential(B) (odd ratio); CI, confidence interval; LD, lactate dehydrogenase.

Table 5. Multivariate logistic regression

Variable	For predicting AKI in burn patients						For predicting early AKI in burn patients					
	B	SE	Wald	Sig	Exp(B)	95% CI for Exp(B)	B	SE	Wald	Sig	Exp(B)	95% CI for Exp(B)
Age	0.042	0.022	3.586	0.058	1.043	0.999–1.090	0.008	0.029	0.069	0.793	1.008	0.952–1.067
%TBSA burned	0.062	0.020	9.639	0.002	1.064	1.023–1.106	0.056	0.026	4.720	0.030	1.057	1.005–1.112
Inhalation injury	1.311	0.750	3.053	0.081	3.711	0.853–16.151	1.515	0.811	3.495	0.062	4.551	0.929–22.288
LD	0.930	0.760	1.496	0.221	2.533	0.571–11.234	0.971	0.948	1.049	0.306	2.641	0.412–16.942
Lactic acid	0.170	0.675	0.063	0.802	1.185	0.316–4.447	–0.426	0.889	0.230	0.632	0.653	0.114–3.728
Serum creatinine	0.983	0.654	2.258	0.133	2.672	0.741–9.630	2.005	0.898	4.978	0.026	7.423	1.276–43.183
AST	–0.829	0.792	1.095	0.295	0.436	0.092–2.062	0.428	1.001	0.183	0.669	1.535	0.216–10.923
Serum myoglobin	0.302	0.757	0.159	0.690	1.353	0.307–5.963	10.314	10.195	1.208	0.272	3.720	0.357–38.702
Myoglobinuria	0.503	0.808	0.388	0.533	1.654	0.340–8.059	1.717	1.126	2.325	0.127	5.566	0.613–50.570

AKI, acute kidney injury; B, b coefficient; SE, standard error; Sig, significance (P-value); Exp(B), Exponential(B) (odd ratio); CI, confidence interval; TBSA, total body surface area; LD, lactate dehydrogenase.

Uni- and multivariate logistic regression analysis prediction AKI and early AKI

Using univariate logistic regression analysis, we analyzed the predictive power of each biomarker on diagnosis of AKI. LD (adjusted odds ratio [OR], 5.060), lactic acid (adjusted OR, 4.879), serum creatinine and serum myoglobin were found to be significant predictors of AKI (Table 4) and LD (adjusted OR, 6.333), serum creatinine (adjusted OR, 8.708), AST (adjusted OR, 6.504), serum myoglobin, lactic acid and cystatin C were found to be significant predictors of early AKI (Table 4). We further analyzed the significant variables and known risk factors (age, percentage of TBSA burned, and inhalation injury) using multivariate logistic regression, and revealed that only percentage of TBSA burned was significant associated with development of AKI (Table 5) and percentage of TBSA burned and serum creatinine were significantly associated with development of early AKI (Table 5).

DISCUSSION

In our study, the prevalence of AKI and mortality rates were as high as 56.5% and 64.6%, respectively. Mortality rates of early AKI are higher than late AKI (72.0% *vs.* 56.5%), although there was no significant difference. This is higher than the prevalence and mortality rates reported in a recent systematic review by Brusselaers et al. [20] who reported that median prevalence was 26.6% (range, 18.4%–47.4%) and median mortality was 34.9% (range, 28.4%–52.6%). They were not such higher in consideration of the population included in our study, which was limited to patients admitted to BICU, not to the general Burn Center, but the prevalence and mortality rate is still higher in major burn patients.

AKI related with burn patients is generally divided into early and late AKI depending on the time of onset [2]. Standard number of days of early and late onset AKI is 5 days after injury, and they have different etiologic factors. The common cause of early AKI is due to reduced cardiac output caused by inadequate fluid resuscitation but may also result from substantial breakdown of muscle enzyme or hemolysis during the first 24 hours after injury. Several studies have advocated that early adequate fluid resuscitation can prevent or minimize the development of AKI because delayed fluid therapy causes decreased renal blood flow and has been found to be related with a poor prognosis in burn patients with AKI [21,22].

Late AKI has several causes and is generally related with nephrotoxic agents, sepsis, and multiple organ failure [2,4,22,23]. Because AKI caused by nephrotoxic agents, such as aminoglycosides and vancomycin, is commonly nonoliguric and doesn't show severe clinical manifestation, the treatment is discontinuous nephrotoxic agents until renal function is recovered [2]. On the other hand, since burn patients with sepsis have a high risk of AKI and relate with poor prognosis, the key treatment is prevention and early recognition of the septic state [5], and identification of the offending organism and early directed-goal therapy should be initiated [24]. All types of AKI are still important causes of complications, which are associated with increased morbidity and mortality [3,25]. So it is vital to identify the biomarkers predicting AKI and select appropriate treatments.

The predictive Safety Testing Consortium Nephrotoxicity Working Group suggested several criteria as key characteristics of a renal safety biomarker [10]. These were as follows: (1) identifies kidney injury early (well before the renal reserve is dissipated and levels of serum creatinine increase), (2) reflects the degree of toxicity, in order to characterize dose dependencies, (3) displays similar reliability across multiple species, including humans, (4) localizes site of kidney injury, (5) tracks progression of injury and recovery from damage, (6) is well characterized with respect to limitations of its capacities, (7) is accessible in readily available body fluids or tissues. Variable biomarkers in accordance with these criteria have been introduced in recent studies [10]. In our study, we didn't include recently emerging biomarkers except cystatin C, because we intended to re-evaluate the value of known biomarkers in major burn patients who have different intensity and duration of the inflammatory response, which may last longer than in other critically ill patients.

The level of BUN and serum creatinine is abrupt and sustains high levels during rapid loss of kidney function in critically ill patients with AKI. These two serum biomarkers are commonly used to detect kidney dysfunction in clinical situations but have severe limitations relating to sensitivity and specificity [10]. In our study, BUN was a poor diagnostic biomarker (AUC, 0.541 in AKI, 0.569 in early AKI) but serum creatinine was a reasonable diagnostic marker (AUC, 0.717 in AKI, 0.816 in early AKI) in major burn patients.

LD is most often measured to check for tissue damage. The protein is in many body tissues, especially the heart, liver, kidney, muscles, brain, blood cells, and lungs. CK is assayed as a biomarker of myocardial infarction, AKI with rhabdomyolysis, and muscular dystrophy. AST is also found in the liver, heart, skeletal muscle, kidney, brain and red blood cells, and it is commonly measured clinically as a biomarker for live disease, not kidney injury. Myoglobin is in high concentration in muscle cells, allowing them oxygenation. Since myoglobin is only found in the bloodstream after muscle injury, it has been known as a marker detecting rhabdomyolysis and used as a biomarker predicting AKI related with rhabdomyolysis. In our study, although serum LD level is usually known as a non-specific marker for predicting AKI, LD showed the greatest AUC in diagnosis of AKI and early AKI. And, AST also showed a reasonable diagnostic marker in AKI (AUC, 0.690) and early

AKI (AUC, 0.790). Serum myoglobin showed a reasonable diagnostic marker in early AKI (AUC, 0.759). We considered that it was because of hypovolemic effects resulting from burn shock in the early stages of burn due to fluid sequestration of interstitial space induced by increasing vascular permeability and substantial breakdown of muscle due to direct heat injury to skeletal muscle. It is a different phenomenon compared with other critically ill patients. However, CK was a poor diagnostic marker even though it has been known as a contributor of AKI with rhabdomyolysis [12]. Cystatin C has been used in clinical studies for years and is a representative functional kidney marker [26]. It is a 13.3 kDa cysteine proteinase inhibitor protein that is released into the plasma at a constant rate by all nucleated cells in the body [27,28]. Many studies have shown that the performance of serum Cystatin C for the prediction of AKI is superior to that of serum creatinine in various clinical settings [27-29]. Despite the proven diagnostic superiority of serum Cystatin C for the detection of AKI compared with serum creatinine, there are few studies on this marker in the area of burns and our result was totally different. Serum creatinine showed better AUC than Cystatin C in our study (Table 3).

In summary, AKI is one of the major complications with high morbidity and mortality in major burn patients. The mainstream treatment is early diagnosis and prevention of sustained insults on kidney functions. Therefore, it is important to identify biomarkers predicting the risk of development of AKI. Although newly emerged biomarkers were not included in our study, except Cystatin C, we concluded that LD, lactic acid and serum creatinine were acceptable as diagnostic biomarkers of AKI; and LD, serum creatinine, AST, and serum myoglobin were reasonable as diagnostic biomarkers of early AKI. However, cystatin C was an unfavorable biomarker in major burn patients.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

REFERENCES

1. Chung KK, Lundy JB, Matson JR, Renz EM, White CE, King BT, et al. Continuous venovenous hemofiltration in severely burned patients with acute kidney injury: a cohort study. Crit Care 2009;13:R62.
2. Mustonen KM, Vuola J. Acute renal failure in intensive care burn patients (ARF in burn patients). J Burn Care Res 2008; 29:227-37.
3. Coca SG, Bauling P, Schifftner T, Howard CS, Teitelbaum I, Parikh CR. Contribution of acute kidney injury toward morbidity and mortality in burns: a contemporary analysis. Am J Kidney Dis 2007;49:517-23.
4. Holm C, Horbrand F, von Donnersmarck GH, Muhlbauer W. Acute renal failure in severely burned patients. Burns 1999;25: 171-8.
5. Ibrahim AE, Sarhane KA, Fagan SP, Goverman J. Renal dysfunction in burns: a review. Ann Burns Fire Disasters 2013;26: 16-25.
6. Belgian Outcome in Burn Injury Study Group. Development and validation of a model for prediction of mortality in patients with acute burn injury. Br J Surg 2009;96:111-7.
7. Brusselaers N, Juhasz I, Erdei I, Monstrey S, Blot S. Evaluation of mortality following severe burns injury in Hungary: external validation of a prediction model developed on Belgian burn data. Burns 2009;35:1009-14.
8. Colpaert K, Hoste EA. Acute kidney injury in burns: a story of volume and inflammation. Crit Care 2008;12:192.
9. Zager RA, Johnson AC, Becker K. Renal cortical lactate dehydrogenase: a useful, accurate, quantitative marker of in vivo tubular injury and acute renal failure. PLoS One 2013;8:e66776.
10. Bonventre JV, Vaidya VS, Schmouder R, Feig P, Dieterle F. Next-generation biomarkers for detecting kidney toxicity. Nat Biotechnol 2010;28:436-40.
11. Coca SG, Yalavarthy R, Concato J, Parikh CR. Biomarkers for the diagnosis and risk stratification of acute kidney injury: a systematic review. Kidney Int 2008;73: 1008-16.
12. Rodriguez E, Soler MJ, Rap O, Barrios C, Orfila MA, Pascual J. Risk factors for acute kidney injury in severe rhabdomyolysis. PLoS One 2013;8:e82992.
13. Kosmadakis G, Michail O, Filiopoulos V, Papadopoulou P, Michail S. Acute kidney injury due to rhabdomyolysis in narcotic drug users. Int J Artif Organs 2011;34:584-8.
14. Jochmans I, Lerut E, van Pelt J, Monbaliu D, Pirenne J. Circulating AST, H-FABP, and NGAL are early and accurate biomarkers of graft injury and dysfunction in a preclinical model of kidney transplantation. Ann Surg 2011;254:784-91.
15. Westhuyzen J, Endre ZH, Reece G, Reith DM, Saltissi D, Morgan TJ. Measurement of tubular enzymuria facilitates early detection of acute renal impairment in the intensive care unit. Nephrol Dial Transplant 2003;18:543-51.
16. Tobiasen J, Hiebert JM, Edlich RF. The abbreviated burn severity index. Ann Emerg Med 1982;11:260-2.
17. Vincent JL, de Mendonca A, Cantraine F, Moreno R, Takala J, Suter PM, et al. Use of the SOFA score to assess the incidence of organ dysfunction/failure in intensive care units: results of a multicenter, pro-

spective study. Working group on "sepsis-related problems" of the European Society of Intensive Care Medicine. Crit Care Med 1998;26:1793-800.
18. Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P; Acute Dialysis Quality Initiative workgroup. Acute renal failure - definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. Crit Care 2004;8:R204-12.
19. Hanley JA, McNeil BJ. The meaning and use of the area under a receiver operating characteristic (ROC) curve. Radiology 1982;143:29-36.
20. Brusselaers N, Monstrey S, Colpaert K, Decruyenaere J, Blot SI, Hoste EA. Outcome of acute kidney injury in severe burns: a systematic review and meta-analysis. Intensive Care Med 2010;36:915-25.
21. Kellum JA, Levin N, Bouman C, Lameire N. Developing a consensus classification system for acute renal failure. Curr Opin Crit Care 2002;8:509-14.
22. Chrysopoulo MT, Jeschke MG, Dziewulski P, Barrow RE, Herndon DN. Acute renal dysfunction in severely burned adults. J Trauma 1999;46:141-4.
23. Emara SS, Alzaylai AA. Renal failure in burn patients: a review. Ann Burns Fire Disasters 2013;26:12-5.
24. Rivers EP, Coba V, Whitmill M. Early goal-directed therapy in severe sepsis and septic shock: a contemporary review of the literature. Curr Opin Anaesthesiol 2008;21:128-40.
25. Soni SS, Pophale R, Ronco C. New biomarkers for acute renal injury. Clin Chem Lab Med 2011;49:1257-63.
26. Jung YJ, Lee HR, Kwon OJ. Comparison of serum cystatin C and creatinine as a marker for early detection of decreasing glomerular filtration rate in renal transplants. J Korean Surg Soc 2012;83:69-74.
27. Gonzalez F, Vincent F. Biomarkers for acute kidney injury in critically ill patients. Minerva Anestesiol 2012;78:1394-403.
28. Odutayo A, Cherney D. Cystatin C and acute changes in glomerular filtration rate. Clin Nephrol 2012;78:64-75.
29. Cai X, Long Z, Lin L, Feng Y, Zhou N, Mai Q. Serum cystatin C is an early biomarker for assessment of renal function in burn patients. Clin Chem Lab Med 2012;50:667-71.