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Original Article

The application values of urine NGAL and MEDS scores in the prognosis evaluation of patients with sepsis and acute kidney injury

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Abstract: Objective: This study aimed to analyze the urine neutrophil gelatinase-associated lipocalin (NGAL) level and mortality in emergency department sepsis (MEDS) score in the prognosis evaluation of patients with sepsis and acute kidney injury. Methods: Sixty-five patients with sepsis and acute kidney injury admitted to our hospital were included, retrospectively analyzed, tested for urinary NGAL, and scored for MEDS. Results: (1) NGAL, MEDS, and mortality were elevated, and the average survival was shortened as acute kidney injury progressed from stage 1 to 2, and then to stage 3 ($P<0.05$); (2) A linear positive association was observed between the urine NGAL levels and the MEDS scores ($r=0.751$, $P<0.05$); (3) While the predicted sensitivity/specificity based on the urinary NGAL level was slightly higher/lower than the predicted sensitivity/specificity from the MEDS score, the combination of the two achieved a significantly higher sensitivity and specificity than when they were applied separately ($P<0.05$). Conclusion: The combined urinary NGAL levels and MEDS scores have a good application value in the prognosis evaluation and predication values in the mortality of patients with sepsis and acute kidney injury.

Keywords: Sepsis, acute kidney injury, urine NGAL, MEDS, prognosis, evaluation

Introduction

Known as a critical illness prone to acute onset, sepsis results in patients being sent to the emergency department (ED) after they show systemic inflammatory response syndrome [1] induced by infection, etc. It progresses rapidly, and may transform into serious conditions or even septic shock, leading to multiple organ dysfunction syndrome [2] if not quickly and accurately diagnosed, and effectively treated.

It is highly likely that multiple organ dysfunction can result from sepsis, especially in the kidneys, and it can specifically manifest as acute kidney injury with the highest severity among all the complications arising from sepsis [3]. Compared with patients suffering only from sepsis, those with sepsis and acute kidney injury face a higher mortality, approaching 80% [4]. In addition, studies by Mårtensson et al. [5] revealed that over half of acute kidney injuries result from sepsis, and a considerable number of studies agree that acute kidney injury is a major factor in sepsis-related deaths. Therefore, the early diagnosis and prognosis evaluation of acute kidney injuries have a great significance in ensuring that doctors can adjust the treatment plans in a timely manner to reduce the risk of death. In previous studies, the serum creatinine levels and urinary volume monitoring have been described as the main tools in the diagnosis of acute kidney injury, but they are somehow hysteretic and subject to multiple factors. As a result, treatment is delayed and the acute kidney injury progresses into end stage renal diseases [6].

With the gradual progression of research, many a biological marker has been discovered and applied, including neutrophil gelatinase-associated lipocalin (NGAL), Interleukin-18 (IL-18), etc., which express themselves at an elevated level in the blood and urine of patients at the

early stage of acute kidney injury, and such elevation is ahead of the time points when changes are observed in the urinary volume and serum creatinine levels. Therefore, they are significant in the early diagnosis of acute kidney injury [7]. In addition, mortality in emergency department sepsis (MEDS) is a scoring system established to predict the mortality of emergency department sepsis patients. It is more convenient and extensively applicable in the judgment of the severity of conditions in emergency department sepsis patients and the prediction of the fatality rate [8]. This study specifically analyzed the NGAL levels and MEDS scores in the prognosis evaluation of patients with sepsis and acute kidney injury.

Materials and methods

Materials

Sixty-five patients admitted to our hospital from May 2018 to April 2019 due to sepsis and acute kidney injury were included and retrospectively analyzed. (1) Inclusion criteria: The patients were required to be aged over 18 and meet the diagnosis criteria for sepsis [9] and acute kidney injury [10]. They provided informed consent to participate in this study, which was approved by the Ethics Committee of Tangshan People's Hospital. (2) Exclusion criteria: patients under 18, patients with a history of chronic renal insufficiency or manifestations of acute kidney injury before hospitalization, patients with obstructive nephropathy or kidney injury due to other reasons, patients who produced little urine.

Methods

We recorded the patients' clinicopathological data, including age, name, gender, basic diseases, symptoms and manifestations, vital signs, and consciousness. Their accessory examination results were recorded, including their imaging findings and the results of their blood biochemistry and routine testing. The infectious site was preliminarily judged, and MEDS scoring was carried out based on the worst results of the patients' examination indexes on the day of hospitalization.

Observation indexes

MEDS score [11]: 6 points for end stage diseases (carcinoma metastaticum or chronic diseases with a possibility of death over 50% in a month); 3 points for age over 65; 3 points for septic shock (systolic pressure under 90 mmHg after fluid resuscitation); 3 points for a breathing rate >20 times/min or a blood oxygen saturation of artery blood of the finger <90%; 3 points for a platelet count $<150\times10^9$/L; 3 points for rod nuclear neutrophils >5%; 2 points for having a lower respiratory infection; 2 points for living in a home for the elderly before hospitalization; 2 points for a Glasgow coma score (GCS) <15.

Staging of acute kidney injury: according to the staging criteria of Kidney Disease Improving Global Outcomes (KDIGO) [12]: stage 1: the serum creatinine level rose by 1.5 to 1.9 times of the base value, or to ≥26.5 μmol/l with urinary volume <0.5 ml/kg/h (6-12 h); stage 2: the serum creatinine level rose by 2.0 to 2.9 times of the base value with a urinary volume <0.5 ml/kg/h (≥12 h); stage 3: the serum creatinine level rose by 3.0 times of the base value or to ≥353.6 μmol/l or posterior renal replacement therapy began with a urinary volume <0.3 ml/kg/h (≥24 h).

NGAL: 5 ml of clean midstream urine was collected into a tube without pyrogen and endotoxin on the day when the patients were diagnosed with acute kidney injury, centrifuged for 5 min at a rate of 4000 rpm. The supernatant was collected into an Eppendorf tube, sealed, numbered, and placed into a freezer at -20°C for future use. All the samples were placed in a 37°C homothermal water-bath for thawing, and tested for sterility according to the instructions on the test kits, and the NGAL level was determined using the ELISA method.

The patients were subject to clinical observation, and their serum creatinine and urinary volume levels were monitored after hospitalization, and then they were divided into the stage 1 group, the stage 2 group, and the stage 3 group according to the KDIGO staging criteria of acute kidney injury.

Deaths were recorded within 28 days as the patients were transferred to the ICU, and after that, they were divided into the death group and the survival group.

Statistical analysis

The statistical analysis was performed using SPSS 23.0. In the case of numerical data

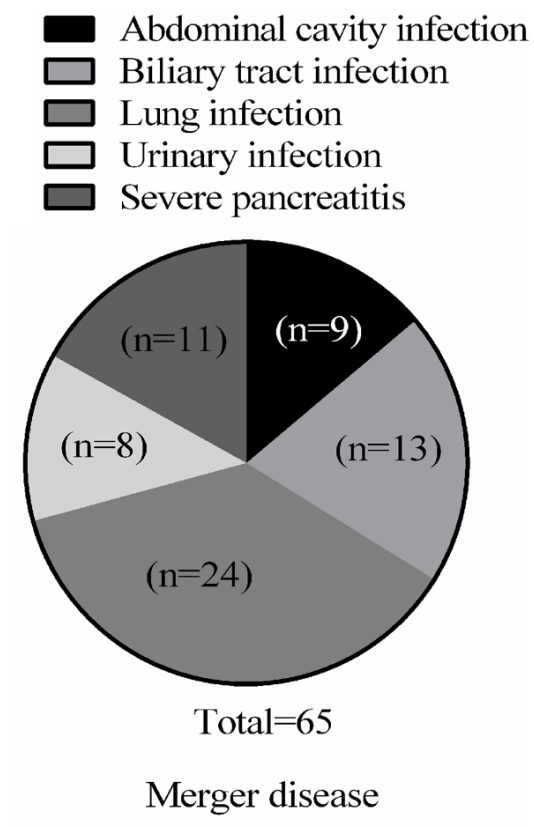

Figure 1. Concurrent diseases in the 65 patients. 9 cases of abdominal infection, 13 cases of infection of biliary tract, 24 cases of pulmonary infection, 8 cases of urinary tract infection, and 11 cases of severe pancreatitis.

expressed as the means ± standard deviations, the intergroup and intragroup comparison studies were carried out using independent-samples *t* tests. In the case of nominal data expressed as [n (%)], the intergroup and intragroup comparison studies were carried out using X^2 tests. Survival curves were drawn in GraphPad Prism 8 in addition to the ROC of the subjects, in order to calculate the area under the curve (AUC), and find the best critical value using the Youden index. For all the statistical comparisons, significance was defined as P<0.05.

Results

Analysis of general materials

Among the 65 patients with sepsis and acute kidney injury, 36 were male and 29 were female, with ages ranging from 32 to 75, and a mean age of (52.36±12.19). For concurrent diseases, 9 of them were suffering from abdominal infections, 13 from infections of the biliary tract, 24 from pulmonary infections, 8 from urinary tract infections, and 11 from severe pancreatitis (**Figure 1**).

Comparison of the patients at different stages of acute kidney injury in terms of NGAL, MEDS and mortality

According to the DKIGO staging criteria, 22/65 of the patients with sepsis and acute kidney injury were in stage 1, 23/65 in stage 2, and 20/65 in stage 3. Urine NGAL, MEDS and mortality rose as the acute kidney injuries progressed from stage 1 to stage 2 and then to stage 3 (P<0.05, **Table 1**).

Comparison of the patients at different stages of acute kidney injury in terms of survival

The average survival shortened as the acute kidney injury progressed from stage 1 to stage 2 and then to stage 3 (P<0.05, **Table 2** and **Figure 2**).

Comparison of the survival group and the death group in terms of NGAL, MEDS, and age

The survival group had lower NGAL levels, MEDS scores, and mean age than the death group (P<0.05, **Table 3**).

Correlation analysis for the urine NGAL and MEDS

To evaluate the correlation of the urinary NGAL levels and the MEDS scores of the 65 patients with sepsis and acute kidney injury, SPSS was adopted to produce a scatter diagram which indicated a linear positive correlation between the urine NGAL and MEDS (r=0.751, *P*<0.05, **Figure 3**).

Prediction values of urine NGAL and MEDS

The values of urine NGAL, MEDS, and their combination in predicting the 4-week mortality of patients with sepsis and acute kidney injury were analyzed according to the ROC, and the results indicated that while the sensitivity/specificity predicted based on urine NGAL was slightly higher/lower than the sensitivity/specificity predicted from MEDS score, the combination of the two achieved a significantly higher sensitivity and specificity than the results when

Table 1. Comparison of patients with sepsis and acute kidney injury at different stages for urinary NGAL, MEDS and mortality

Staging of acute kidney injury	n	NGAL (ng/ml)	MEDS (score)	Mortality [n (%)]
Stage 1	22	113.65±25.85	8.75±2.63	6 (27.27)
Stage 2	23	159.63±50.27*	11.85±2.45*	10 (43.49)*
Stage 3	20	279.54±93.65*,&	16.85±2.41*,&	13 (65.00)*,&
F/X^2		12.536	18.527	6.854
P		0.000	0.000	0.027

Note: *P<0.05 as compared with stage 1, and &P<0.05 as compared with stage 2.

Table 2. Comparison of patients at different stages of acute kidney injury for survival

Staging of acute kidney injury	n	Shortest survival (d)	Longest survival (d)	Average survival (d)
Stage 1	22	9	36	20.16±5.68
Stage 2	23	11	36	14.82±3.29*
Stage 3	20	5	16	9.65±2.15*,&

Note: *P<0.05 as compared with stage 1, and &P<0.05 as compared with stage 2

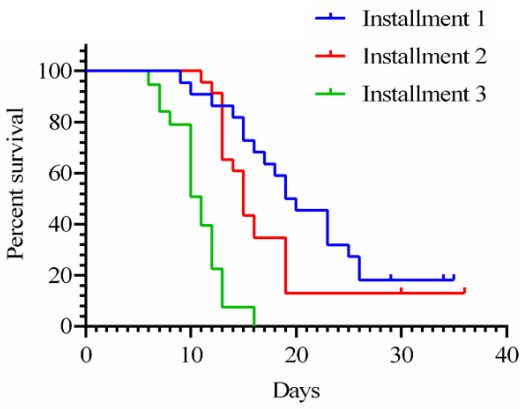

Figure 2. Comparison of the patients at the different stages of acute kidney injury for survival. The average survival shortened as the acute kidney injury progressed from stage 1 to stage 2 and then to stage 3 (P<0.05).

Table 3. Comparison of the survival and death groups for urinary NGAL, MEDS and age

Group	n	NGAL (ng/ml)	MEDS (score)	Mean age (y)
Survival	36	124.19±36.25	9.92±2.46	55.83±6.15
Death	29	232.26±92.27	14.33±3.50	63.57±8.08
t		6.446	5.956	4.386
P		0.000	0.000	0.000

they were applied separately (P<0.05, **Table 4** and **Figure 4**).

Discussion

Sepsis is likely to cause major organ dysfunction and high mortality. Clinically, it has been found that acute kidney injury is the most important factor leading to the deaths of patients with sepsis [13]. A study has reported a positive correlation between acute kidney injury and the mortality of patients with sepsis. Compared with patients who have not suffered from acute kidney injury, patients with sepsis and acute kidney injury generally experience a significant elevation of C-reactive protein, APACHE II scores, and 4-week mortality [14]. Accordingly, if patients with sepsis and acute kidney injury were not evaluated at an early stage or effectively protected and intervened, their kidney functions would deteriorate sharply in a short period of time, leading to a higher demand on renal replacement therapy, a significantly extended hospital length of stay, and increased medical expenses.

As there is no typical clinical manifestation related to acute kidney injury, the degree of kidney injury, the course of the disease, the urinary volume and serum creatinine levels are the principal factors involved in the clinical judgment of acute kidney injury [15]. However, those indexes are not sensitive enough, and the results are subject to many factors, and they cannot provide a guarantee for the early differentiation of kidney injury [16]. After general acute kidney injuries occur, the serum creatinine levels may rise only after several hours or days and cannot be individually depended on to make accurate judgments for kidney function, acute kidney injury, or chronic kidney insufficiency. Therefore, doctors may be unlikely to accurately detect acute kidney injury in the

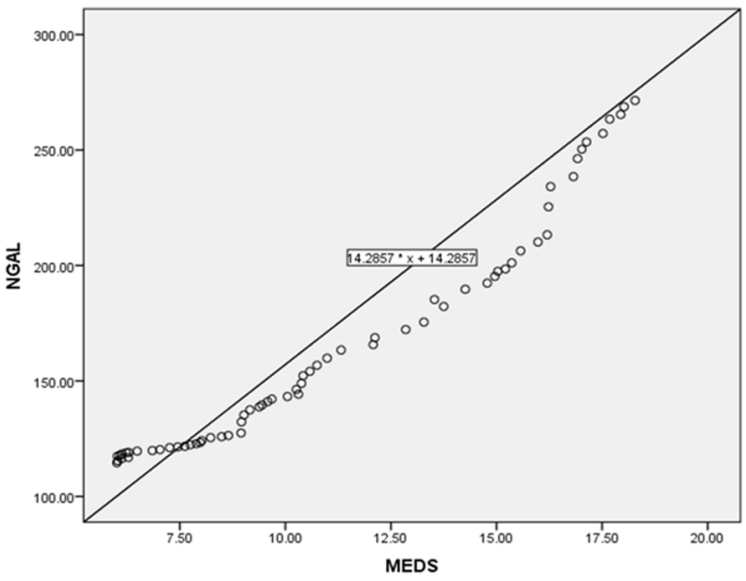

Figure 3. Correlation analysis for urinary NGAL and MEDS. A scatter diagram indicating a linear positive correlation between the urinary NGAL levels and MEDS scores (r=0.751, *P*<0.05).

early stage, such that some patients may miss the best opportunity for treatment, so the disease progresses to end stage kidney disease [17].

Therefore, clinical efforts have been made to find better markers of kidney injury for clinical diagnosis and treatment. Research suggests that it is best to take high-quality markers of kidney injury from the urine. The testing is convenient, the results are precise, and the index changes are closely associated with the degree of kidney injury so as to provide useful guidance for treatment. Furthermore, efficacy and prognosis are evaluated [18]. NGAL is a member from the lipid-carrying protein family, a protein binding on gelatinase-B and a new marker of acute kidney injury in clinical application [19]. Clinically it has been verified that NGAL is related to the immune response, cell differentiation and apoptosis, and the inflammatory response. NGAL is mainly produced in distal tubules and collecting tubes, and then reabsorbed by proximal tubules after filtration through the glomerulus [20]. If the kidneys are ischemic or subject to toxins, NGAL will be expressed at a high level in the epithelium of the injured kidney tubules, and also in the urine due to abnormal absorption [21]. Michalak et al. [22] found that after local ischemic injury in the kidneys, the NGAL level rises significantly. Furthermore, Eilenberg et al. [23] pointed out the elevated dose dependence of NAGL in the urine and blood, and the degree of kidney injury. NGAL is a new biomarker of acute kidney injury which can be detected in the urine and blood at 3 h after a kidney injury. Its level is not affected by the body, extrarenal factors, drugs, or r blood-purification technology [24].

In the past, the evaluation of sepsis was based on APACHE II, but the MEDS system is designed more in accordance with the characteristics of patients with emergency department infections. The comparative study by Pong et al. [11] showed that to predict the 4-week mortality of patients with sepsis, MEDS demonstrated a better predication value than APACHE II. According to the studies by Zhao et al. [25], in which, MEDS, APACHE II and blood lactate were compared, MEDS had the best specificity and positive and negative prediction values. Based on the findings in this study, as the acute kidney injuries progressed to a more advanced stage, the MEDS and urine NGAL also gradually rose, and survival shortened. In addition, a comparison between surviving and deceased patients found that the MEDS and urine NGAL in patients who survived were significantly lower than in the patients who died. An analysis of the predication values revealed that, while the sensitivity/specificity predicted based on urine NGAL was slightly higher/lower than it was from MEDS score, the combination of the two achieved a significantly higher sensitivity and specificity than the results when they were applied separately (P<0.05). Therefore, the value of MEDS and urine NGAL in combination was analyzed. Though urine NGAL can predict the progress of sepsis and acute kidney injury more accurately, it fails with the severity of patients with sepsis. The combination with MEDS forms a mutually supplemented portfolio with higher values.

In conclusion, urine NGAL and MEDS have better application values in the prognosis evalua-

Table 4. Prediction values of urinary NGAL and MEDS in patient mortality

Index	AUC (95% CI)	Standard error	Progressive significance	Progressive 95% CI	
				Lower limit	Upper limit
Urine NGAL	0.702	0.066	0.005	0.573	0.831
MEDS	0.664	0.068	0.024	0.531	0.796
Urine NGAL+MEDS	0.913	0.040	0.000	0.836	0.991

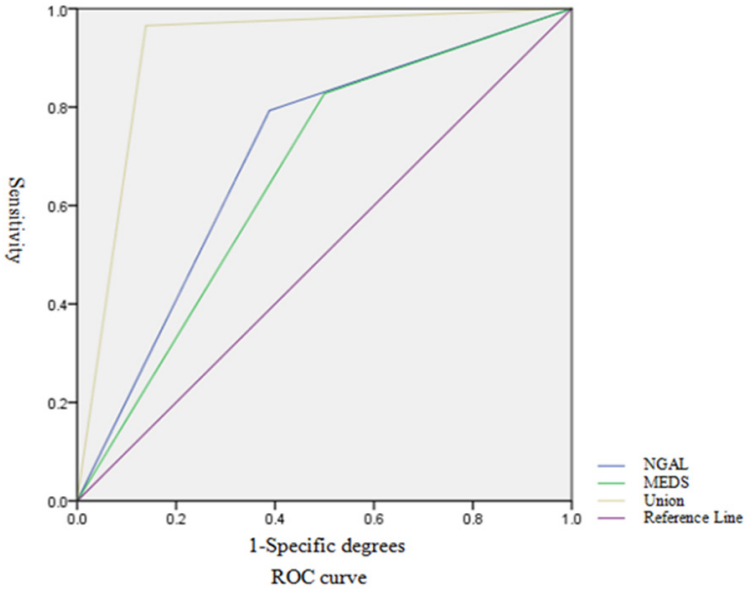

Figure 4. The prediction values of the urinary NGAL levels and MEDS scores in terms of mortality. The 28-day death AUC was 0.702 (*P*=0.005) if predicated by urinary NGAL, 0.664 (P=0.024) if predicated by MEDS, and 0.913 (P=0.000) if predicated by urine NGAL+MEDS.

tion, and predication values in the death of patients with sepsis and acute kidney injury. But this retrospective study, failed to screen the study objects in advance, and the limited sample size resulted in an insufficiently comprehensive analysis of the study results, and less representative results. Our future studies will be based on larger sample sizes and from more aspects to achieve a certain depth, and they will be forward looking to obtain more scientific and representative study conclusions to provide more useful information for the condition evaluation and treatment guidance on patients with sepsis and acute kidney injury.

Disclosure of conflict of interest

None.

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References

[1] Rello J, Valenzuela-Sánchez F, Ruiz-Rodriguez M and Moyano S. Sepsis: a review of advances in management. Adv Ther 2017; 34: 2393-2411.

[2] Faix JD. Biomarkers of sepsis. Crit Rev Clin Lab Sci 2013; 50: 23-36.

[3] Ludwig KR and Hummon AB. Mass spectrometry for the discovery of biomarkers of sepsis. Mol Biosyst 2017; 13: 648-664.

[4] Gómez H and Kellum JA. Sepsis-induced acute kidney injury. Curr Opin Crit Care 2016; 22: 546-553.

[5] Mårtensson J and Bellomo R. Sepsis-induced acute kidney injury. Crit Care Clin 2015; 31: 649-660.

[6] Kellum JA, Sileanu FE, Murugan R, Lucko N, Shaw AD and Clermont G. Classifying AKI by urine output versus serum creatinine level. J Am Soc Nephrol 2015; 26: 2231-2238.

[7] Sivalingam Z, Larsen SB, Grove EL, Hvas AM, Kristensen SD and Magnusson NE. Neutrophil gelatinase-associated lipocalin as a risk marker in cardiovascular disease. Clin Chem Lab Med 2017; 56: 5-18.

[8] Sherwin R, Winters ME, Vilke GM and Wardi G. Does early and appropriate antibiotic administration improve mortality in emergency department patients with severe sepsis or septic shock? J Emerg Med 2017; 53: 588-595.

[9] Nunnally ME. Sepsis for the anaesthetist. Br J Anaesth 2016; 117 Suppl 3: iii44-iii51.

[10] Levey AS and James MT. Acute kidney injury. Ann Intern Med 2017; 167: ITC66-ITC80.

[11] Pong JZ, Koh ZX, Samsudin MI, Fook-Chong S, Liu N and Ong MEH. Validation of the mortality in emergency department sepsis (MEDS) score in a Singaporean cohort. Medicine (Baltimore) 2019; 98: e16962.

[12] Goodship TH, Cook HT, Fakhouri F, Fervenza FC, Frémeaux-Bacchi V, Kavanagh D, Nester CM, Noris M, Pickering MC, Rodríguez de Cór-

doba S, Roumenina LT, Sethi S and Smith RJ; Conference Participants. Atypical hemolytic uremic syndrome and C3 glomerulopathy: conclusions from a "kidney disease: improving global outcomes" (KDIGO) controversies conference. Kidney Int 2017; 91: 539-551.
[13] Alobaidi R, Basu RK, Goldstein SL and Bagshaw SM. Sepsis-associated acute kidney injury. Semin Nephrol 2015; 35: 2-11.
[14] Keir I and Kellum JA. Acute kidney injury in severe sepsis: pathophysiology, diagnosis, and treatment recommendations. J Vet Emerg Crit Care (San Antonio) 2015; 25: 200-209.
[15] Gaffney AM and Sladen RN. Acute kidney injury in cardiac surgery. Curr Opin Anaesthesiol 2015; 28: 50-59.
[16] Petejova N and Martinek A. Acute kidney injury due to rhabdomyolysis and renal replacement therapy: a critical review. Crit Care 2014; 18: 224.
[17] Moledina DG and Parikh CR. Phenotyping of acute kidney injury: beyond serum creatinine. Semin Nephrol 2018; 38: 3-11.
[18] Kellum JA. Diagnostic criteria for acute kidney injury: present and future. Crit Care Clin 2015; 31: 621-632.
[19] Vittori M, Baroni S, Ferraro PM, Gambaro G, Morelli R, Bassi P and D'Addessi A. Neutrophil gelatinase-associated lipocalin (NGAL) value changes before and after shock wave lithotripsy. Urolithiasis 2017; 45: 347-351.
[20] Forster CS and Devarajan P. Neutrophil gelatinase-associated lipocalin: utility in urologic conditions. Pediatr Nephrol 2017; 32: 377-381.
[21] Kiseli M, Caglar GS, Yilmaz H, Gursoy AY, Candar T, Pabuccu EG, Bengisun ZK and Tuzuner F. Neutrophil gelatinase-associated lipocalin levels during pneumoperitoneum. JSLS 2017; 21.
[22] Michalak Ł, Bulska M, Kudłacz K and Szcześniak P. Role of oncogene 24p3 neutrophil gelatinase-associated lipocalin (NGAL) in digestive system cancers. Postepy Hig Med Dosw (Online) 2016; 70: 1026-1031.
[23] Eilenberg W, Stojkovic S, Piechota-Polanczyk A, Kaider A, Kozakowski N, Weninger W, Nanobachvili J, Wojta J, Huk I, Demyanets S and Neumayer C. Neutrophil gelatinase associated lipocalin (NGAL) is elevated in type 2 diabetics with carotid artery stenosis and reduced under metformin treatment. Cardiovasc Diabetol 2017; 16: 98.
[24] Macdonald SP, Arendts G, Fatovich DM and Brown SG. Comparison of PIRO, SOFA, and MEDS scores for predicting mortality in emergency department patients with severe sepsis and septic shock. Acad Emerg Med 2014; 21: 1257-1263.
[25] Zhao Y, Jia Y, Li C, Fang Y and Shao R. The risk stratification and prognostic evaluation of soluble programmed death-1 on patients with sepsis in emergency department. Am J Emerg Med 2018; 36: 43-48.