Assessment of the diagnostic ability of RIFLE and SOFA scoring systems in comparison with protein biomarkers in acute kidney injury

https://doi.org/10.1515/labmed-2018-0099
Received July 25, 2018; accepted November 3, 2018

Abstract

Background: We aimed to assess the diagnostic sensitivity of Risk, Injury, Failure, Loss, and End-stage (RIFLE) and Sequential Organ Failure Assessment (SOFA) scoring systems regarding the serum creatinine level in acute kidney injury (AKI) patients hospitalized in the intensive care unit (ICU). This study also aims to compare the sensitivity of these scoring systems with that of mitochondrial pyruvate carrier 1 (MPC-1), interleukin-10 (IL-10) and neutrophil gelatinase-associated lipocalin (NGAL) as biomarkers.

Methods: This is a cross-sectional study. Thirty patients with increased creatinine level and decreased urine output were recognized as AKI patients, and 30 patients were selected as the control group. The serum levels of each of the proteins of interest were measured at the initial state (moment of entrance) and final state (14th day in the ICU). Statistical analysis was performed with respect to t-test, and a p-value < 0.05 was considered significant. The diagnostic ability of biomarkers was assessed using receiver operating characteristic (ROC) curve.

Results: The majority of patients were recognized in the risk level of RIFLE, and level 1 of SOFA scoring system. There was no correlation between RIFLE and SOFA (p = 0.123). The expression of MPC-1, IL-10 and NGAL was more remarkable compared with the serum creatinine level. The ROC area change for MPC-1 and IL-10 was higher compared with that for NGAL. As a result, MPC-1 and IL-10 are more reliable biomarkers than NGAL to predict the incidence of AKI in the earlier stage.

Conclusions: There was no significant correlation between SOFA and RIFLE classification, and also the sensitivity of these scoring systems was identified at the risk level for AKI patients. Instead, the level of biomarkers alters earlier, and in higher concentration, than creatinine and urine output changes; therefore, they are more reliable than RIFLE and SOFA scoring systems for prognosis purposes.

Keywords: acute renal injury; biomarker; RIFLE; SOFA.

Introduction

Acute kidney injury (AKI) is a frequent complication affecting approximately 10% of patients with acute illnesses requiring hospitalization [1]. AKI is the reason for increased morbidity, length of stay in the hospital and an enhancement in hospital mortality up to 9 times greater in patients with AKI than in patients without AKI [2–5]. The occurrence of AKI has also been related to increased risks of chronic kidney disease (CKD), stroke and other cardiovascular events [6, 7]. Approximately 4% of patients with AKI have been shown to require renal replacement therapy, and because of hemodynamic instability they
might need to receive continuous renal replacement therapy (CRRT) frequently [8, 9]. As AKI is economically expensive and incurs extra cost for patients, it is a target to both improved patient and health economic outcomes [2]. According to pieces of evidence, even minor changes in serum creatinine in AKI patients are associated with increased mortality [4].

Risk, Injury, Failure, Loss, and End-stage (RIFLE), a multilevel classification system, was proposed to cover a complete spectrum of acute renal dysfunction, including Risk of renal dysfunction, Injury to the kidney, Failure or Loss of kidney function and End-stage kidney disease (under the acronym of RIFLE) [5]. Originally, the aim of RIFLE classification was to standardize the definition and severity of AKI, rather than be a tool to predict mortality. Sequential Organ Failure Assessment (SOFA) score is another method to track a person’s status during the stay in the intensive care unit (ICU) and has been used to measure the effectiveness of renal therapy [10, 11]. However, these methods are not without limitations. For instance, risk patients defined by creatinine criteria are more severely ill compared with risk patients defined by urine output criteria (not well balanced) [12, 13]. Another limitation of RIFLE is the need for baseline creatinine, which may not always be available [14, 15]. Therefore, there is a need for more accurate and reliable methods to not only assess the severity and mortality but also for diagnosis.

Many biomarkers have been proposed, including neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1 (KIM-1), interleukin-18 (IL-18), cystatin C, angiotensigen and renin, as early markers of AKI, which may be useful for the detection of AKI before increases in serum creatinine [16–20]. Monocyte chemoattractant protein 1 (MCP-1) is a cytokine that activates monocytes and various inflammatory processes [21]. MCP-1 has shown a very strong relation with the progression of renal disease, which has been verified by preclinical studies proving that the blockade of the MCP-1 receptor (chemokine receptor 2 [CCR2]) reduces interstitial fibrosis [22, 23]. IL-10 is a multifunctional cytokine produced by a variety of other cells [24], which regulates proliferation, differentiation and function of immune, dendritic cells and endothelial cells in response to inflammatory/immune stimulation [25–27]. The diagnostic ability of NGAL in AKI has been assessed for a decade [28]. Kidney epithelial cells, in a stressed condition, predominantly secrete monomeric NGAL. Also, elevated urinary homodimeric levels and abundance of monomeric NGAL in AKI patients support this fact [29, 30]. In this study, we aimed to assess the diagnostic ability and sensitivity of RIFLE and SOFA scoring systems regarding the serum creatinine level and to compare these classification systems with the diagnostic sensitivity of MCP-1, IL-10 and NGAL as biomarkers for AKI.

Materials and methods

Patients

This cross-sectional study was performed with 60 patients who were hospitalized in the ICU. Thirty patients with increased creatinine level and reduced urine output (as per AKI criteria) were selected as the case group, and the other 30 patients were selected as the control group.

Inclusion and exclusion criteria

Patients older than 18 years and with AKI features (increased serum creatinine level, reduced urine volume), whose serum was available, were included in this study. Patients with a history of CKD, end-stage renal disease (ESRD) and kidney transplant were excluded from this study.

Performance

Blood samples were collected in five steps after ICU hospitalization (at the moment of entrance, 1st, 3rd, 7th and 14th day), each specimen was of 5 mL. Blood serum was separated by centrifugation and stored in −80 °C. Serum creatinine level and urine output were measured daily and every 6 h, respectively. Patients with a creatinine level 1.5-fold of baseline and urine volume less than 0.5 mL/kg/6 h were selected for the measurement of the serum level of IL-10, NGAL and MCP-1. Also, RIFLE classification and SOFA score variables such as PaO₂, FiO₂, Glasgow Coma Scale (GCS), blood pressure, bilirubin level and blood platelet counts were measured daily.

Ethical consideration

The study was carried out in accordance with the Declaration of Helsinki, and the Ethics Committee of the Sari University of Medical Sciences approved the protocol of this study. The study procedure and probable side effects...
were explained to the patient and written consent was acquired. The patients’ records were kept confidential.

Data analysis

Quantitative data were reported as mean ± standard deviation. Statistical analysis was performed with respect to T-test and a p-value < 0.05 was considered significant. The diagnostic ability was analyzed using receiver operating characteristic (ROC) curve, sensitivity and specificity as true positive and false positive, respectively. The cut-off point was determined from the curve. All data were analyzed using IBM SPSS Statistics for Windows, version 19.0 (SPSS Inc., Chicago, IL, USA).

Results

In the present study, among the case group patients, 56.67% of the patients were male and 43.33% of the patients were female. In the control group, 64.3% were male and 35.7% were female. According to chi-squared analysis, the gender difference between the two groups was not significant (p = 0.553). Also, the average age in the case and control groups was 61.46 ± 21.57 and 60.57 ± 20.21, respectively, and according to t-test analysis, the age difference between the case and control groups was not statistically significant (p = 0.872).

The severity of AKI in ICU patients based on SOFA and RIFLE scores is presented in Table 1. The RIFLE score was assessed in three levels (Risk, Injury, Failure) and by considering the creatinine level and urine output. Nonetheless, 21 (70%) patients were categorized with Risk exposure, eight (27%) patients with Injury exposure and one (3%) with Failure exposure. According to SOFA score, 19 patients obtained score 1 (creatinine 1.2–1.9 mg/dL), three patients obtained score 2 (creatinine 2–3.4 mg/dL), one patient obtained score 3 (creatinine 3.5–4.9 mg/dL) and the rest obtained score 0 (creatinine below 1.2 mg/dL). There was no significant correlation between RIFLE and SOFA score classification (p = 0.123).

Comparison of the level of biomarkers in the baseline state did not show any significant differences between the case and control groups. On the other hand, our results demonstrated that in the final state there was a significant difference between the case and control groups in terms of the level of biomarkers. Comparing the case group in the baseline and final state showed a statistically significant difference. On the contrary, no significant difference was observed in the control group at different states, except for MCP-1 which showed a significant decrease in the final state (p = 0.003) (Table 2).

ROC analysis provides us with information regarding the diagnostic ability of candidate biomarkers. The ROC profile was obtained for MCP-1, IL-10 and NGAL (Figure 1). The area under the ROC curve, cut-off, sensitivity and specificity for biomarkers are summarized in Table 2. The ROC area change for mitochondrial pyruvate carrier 1 (MPC-1) and IL-10 was higher compared to that for NGAL.

Discussion

There is considerable concern about AKI, as it is expensive and associated with a high rate of mortality, and increasingly policy guidelines suggest predicting AKI mortality [2]. In the UK, the actual incidence of AKI was difficult to assess until there were robust electronic patient records in all hospitals. According to previously documented in-hospital mortality, the rate of mortality associated with AKI incidence was recognized as very high compared to a population of patients without AKI [4, 5].

Therefore, it is necessary to establish an efficient method for the early detection of AKI incidence. RIFLE and SOFA score classification have been widely used to predict the mortality of AKI [31–34]. In a study on children with AKI, the maximum RIFLE score for half of the patients was achieved within 24 h, and 75% achieved the maximum score after a 7-day stay at the ICU, and finally, the authors of this study related the RIFLE scores to increased mortality [35]. Furthermore, the expression of creatinine, which is the main monitoring factor to achieve RIFLE and SOFA, almost occurs at low concentration levels [36, 37]. In a study by Chang et al. on patients concomitant with AKI admitted to the ICU, they recommended the application of SOFA by physicians to assess ICU mortality due to its
practicality and low cost. They mentioned that a SOFA score of \( \geq 11 \) on ICU day 1 should be considered an indicator of negative short-term outcomes [38]. In other words, SOFA and RIFLE are more suitable to standardize the definition and severity of AKI rather than for prognosis purposes, because of the non-sensitivity of serum creatinine which is the core criterion for SOFA and RIFLE classification. In the same way, the results of the present study demonstrated that the majority of patients were localized in the risk level of RIFLE and level 1 of SOFA; in other words, the detection limit for RIFLE and SOFA, in best condition, is in level 1, and not less. However, no correlation was observed between SOFA and RIFLE \((p = 0.123)\) (Table 1). This results reinforced the necessity of existence of other factors to diagnose AKI in early stages.

In this study, we investigated the diagnostic ability of MPC-1, IL-10 and NGAL as biomarkers for AKI incidence in early stages. It has been shown that the MPC-1 concentration was higher in kidney donors with AKI in comparison with donors without AKI [39]. Also, MCP-1 expression in mice peaks several days after inducing renal ischemia/reperfusion (I/R) injury coinciding with macrophage accumulation followed by significantly decreased survival and increased renal damage within the first 2 days [40]. Similarly, the results of the present study demonstrated that the MPC-1 level increased significantly in the case group in the final state, which confirms the association between AKI incidence and expression of MPC-1. However, in the control group, the MPC-1 level decreased in the final state, which can be attributed to the decrease of inflammation in patients. In this study, the ROC area in the initial state was 0.52, which increases to 0.73 in the final state. Therefore, MPC-1 can be reliably used to predict AKI.

As our results demonstrated, the IL-10 level decreased in AKI patients in the final state of ICU stay. On the contrary, in a study on induced aging rates, the mortality was associated with increased severity of septic AKI and an increased inflammatory response including IL-10 [41]. Also, administration of very high doses of endotoxin has shown sustained AKI and increased serum IL-10 level in 4 h, which implied the potential association between AKI and IL-10 [42]. The predicting ability of IL-10 was found to be reliable as the ROC area in the final state was 0.75 and more than that in the initial state (ROC area 0.51).

During the last decade, genomic analyses have shown upregulated NGAL gene after ischemic AKI, and so, NGAL has become a possible marker for the early detection of AKI [28, 43]. Also, studies on critically ill patients have consistently shown an association with NGAL levels in plasma or urine and severity of established AKI [44–46]. In the same way, our results demonstrated a significant increase in the NGAL level in AKI patients \((p = 0.015)\). Kashani et al. [44] obtained only a limited performance (ROC area 0.69) when NGAL was used to predict severe AKI; however, our performance was slightly better (ROC area 0.72), and there was no considerable difference compared to the initial state.

In conclusion, this study showed no significant correlation between SOFA and RIFLE classification, and also the higher sensitivity of these scoring systems was identified at risk level 1 for AKI patients. Furthermore, we
demonstrated a significant serum level alteration for each of MPC-1, IL-10 and NGAL in patients with AKI. The levels of these proteins alter earlier than creatinine and urine output changes; therefore, they are more reliable than RIFLE and SOFA scoring systems for prognosis purposes. MPC-1 and IL-10 are more reliable biomarkers as the ROC area for these proteins was higher in the final state compared with that in the initial state.

Acknowledgments: This study was the graduation thesis of Dr. Mohamadmehdi Kordjazi for his specialization degree in internal medicine. We obtained a grant from Molecular and Cell Biology Research Center of Mazandaran University of Medical Sciences.

Author contributions: All the authors have accepted responsibility for the entire content of this submitted manuscript and approved submission.

Research funding: None declared.

Employment or leadership: None declared.

Honorarium: None declared.

Competing interests: The funding organization(s) played no role in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the report for publication.

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