J Renal Inj Prev. 2022; 11(2): e32043.

http://journalrip.com doi: 10.34172/jrip.2022.32043

Journal of Renal Injury Prevention

Evaluation of the possibility of using urinary neutrophil gelatinase-dependent lipocalin as a predictor of acute kidney injury in intensive care unit patients

Sepideh Hajian[1], **Nafiseh Rastgoo**[2*], **Sanaz Jamshidi**[2]

[1]Clinical Research Development Unit, Velayat Hospital, Qazvin University of Medical Sciences, Qazvin, Iran
[2]Student Research Committee, Qazvin University of Medical Sciences, Qazvin, Iran

ARTICLE INFO

Article Type:
Original

Article History:
Received: 10 March 2022
Accepted: 30 April 2022
Published online: 6 May 2022

Keywords:
Acute kidney injury, Intensive care unit, Urinary neutrophil gelatinase-dependent lipocalin

ABSTRACT

Introduction: Due to the increase in the incidence of acute kidney injury (AKI), especially in patients admitted to the intensive care unit (ICU), its occurrence has been studied using biomarkers such as urinary neutrophil gelatinase-dependent lipocalin (uNGAL). However, its clinical utility has not yet been approved.

Objectives: This study aimed to investigate the possibility of using uNGAL as a predictor of AKI in patients admitted to the ICU.

Patients and Methods: This prospective study was conducted on 32 patients admitted to the ICU who had normal creatinine level at the ICU admission and did not fulfill the RIFLE (risk, injury, failure, loss of kidney function, and end-stage kidney disease) criteria. Initially, creatinine level and the sequential organ failure assessment (SOFA) score were recorded. In the first 24 hours of hospitalization, urine samples were taken from patients to assess uNGAL levels. In the following days, creatinine levels and the day of its rise were recorded. The incidence of AKI was assessed based on the RIFLE criteria, and the relationship between the AKI incidence and the uNGAL level at admission was assessed.

Results: The mean (SD) of patients' age was 63 ± 17 years, and 18 patients (56%) were male. The cause of hospitalization was post-cardiac surgery in 21 patients (66%). The median SOFA score of patients was 2.5 at admission. According to the RIFLE criteria, 47% of patients had kidney problems at different stages. The median length of hospital stay was 13 days, while four patients (13%) died. Range and mean (SD) of uNGAL level at admission in all patients was 46.1 to 172.5 ng/mL and 89.94 ± 30.9 ng/mL, respectively, which was not significantly different between the two sexes and between living and deceased patients. Although the mean of uNGAL increased in patients in the risk and injury stage of the RIFLE criteria compared to normal patients, the difference between them was not significant. The increase in uNGAL was directly related to the increase in SOFA score (Spearman's rho = 0.360, $P = 0.043$), while its changes was not significantly related to age or creatinine elevation ratio.

Conclusion: The findings of our study showed that, in ICU admitted patients, first-day uNGAL level was not helpful in predicting AKI based on the RIFLE criteria.

Implication for health policy/practice/research/medical education:
Various studies have reported that the use of urinary or serum neutrophil gelatinase-related lipocalin (NGAL) in the diagnosis and management of acute kidney injury (AKI) may improve patient outcomes, however other studies have not confirmed its clinical utility. Our findings showed that, in 32 patients admitted to the intensive care unit (ICU), first-day urinary NGAL (uNGLA) level was not helpful in predicting AKI based on the RIFLE (risk, injury, failure, loss of kidney function, and end-stage kidney disease) criteria.

Please cite this paper as: Hajian S, Rastgoo N, Jamshidi S. Evaluation of the possibility of using urinary neutrophil gelatinase-dependent lipocalin as a predictor of acute kidney injury in intensive care unit patients. J Renal Inj Prev. 2022; 11(2): e32043. doi: 10.34172/jrip.2022.32043.

***Corresponding authors**: Nafiseh Rastgoo, Email: nafis.rastgoo.20@gmail.com, n.rastgo@qums.ac.ir

Original

Introduction

Acute kidney injury (AKI) is a common complication with a growing incidence in patients admitted to the intensive care unit (ICU) that is associated with significant mortality and morbidity (1). AKI is defined by the Kidney Disease Guidelines: Improving Global Outcomes (KDIGO) as an increase in serum creatinine and/or a decrease in urinary output (2). Moreover, there are other classifications such as RIFLE (risk, injury, failure, loss of kidney function, and end-stage kidney) and AKIN (acute kidney injury network) criteria to determine its severity (3,4). AKI is associated with increased mortality in ICU patients and an increased need for renal replacement therapy (5). Serum creatinine level is related to some factors such as age, diet, and muscle mass; it increases only if the glomerular filtration rate (GFR) is decreased by more than 50% (6). On the other hand, early detection of patients at risk for AKI may provide an opportunity to perform some interventions to prevent the onset and progression of AKI (7); thereby, the research for finding biomarkers for early detection of AKI is considered.

Various biomarkers such as cystatin C, interleukin-18 (IL-18), and neutrophil gelatinase-related lipocalin (NGAL) have been studied to predict AKI development in different patients (8,9). NGAL can be measured in both serum and urine (10). Urinary NGAL (uNGAL) is highly expressed in damaged renal tubules and can be detected rapidly in urine (11). Although various studies in the last decade have reported that the use of urinary or serum NGAL in the diagnosis and management of AKI may improve patient outcomes (12,13), some other studies have not confirmed its clinical use, and further studies in this area have been recommended (14,15). For example, Koeze et al, investigated ICU admitted patients and reported that although plasma NGAL was significantly higher at baseline in patients progressing to AKI, adding it to the AKI prediction model did not improve prognosis (16).

Objectives

Given that the use of new biomarkers is associated with high costs and their clinical use has not yet been definitively confirmed, the present study aimed to investigate the possibility of using uNGAL as a predictor of AKI in ICU admitted patients.

Patients and Methods

This prospective study was performed on 32 patients admitted to the ICU of three hospitals of Bu Ali Sina, Velayat, and Rajai in Qazvin. The patients had normal creatinine level at ICU admission and did not fulfill the RIFLE criteria (risk, injury, failure, loss, and end-stage kidney). Patients' data were recorded at the time of admission, including age, gender, history of dialysis, nephrotic syndrome and cardiovascular disease, creatinine level, and SOFA (sequential organ failure assessment) score. During the first 24 hours of hospitalization, urine samples were taken from the patients, and the samples were transferred to the laboratory. The samples were centrifuged at 2000 rpm for 5 minutes to prepare supernatant for uNGAL level measurement and were kept at -80°C. In the following days, creatinine level, day of creatinine rise, length of hospital stay, and mortality were recorded.

The incidence of AKI was assessed based on the RIFLE criteria, which is an accepted standard for preventing and treating AKI. According to these criteria, a 1.5 times increase in creatinine level is simply considered as risk, 2 times increase considered as injury, and 3 times increase or increase more than 0.5 mg/dL if the creatinine is more than 4 mg/dL or more is considered as failure (3).

After collecting 32 samples, the uNGAL level of the urine sample was measured by 48 human neutrophil gelatinase-associated lipocalin (enzyme-linked immunosorbent assay) kit (Hangzhou Eastbiopharm Company, China). Finally, the relationship between the incidence of AKI based on RILFE criteria and the level of uNGAL at admission was investigated.

Data analysis

SPSS version 25 statistical software was used for data entry and analysis. Frequency (percentage) was conducted to describe qualitative data. The mean (standard deviation), median and interquartile range (IQR) were utilized to describe quantitative variables. Independent sample *t* test and one-way ANOVA were employed to compare uNGAL levels. Pearson's and Spearman's correlation coefficients were also conducted to evaluate the correlation between uNGAL and age, SOFA score, and creatinine elevation. Accordingly, $P<0.05$ was considered statistically significant.

Results

Table 1 shows the characteristics of patients. Table 2 shows the kidney status of patients at the time of admission to the ICU and during the hospital stay. According to the RIFLE criteria, 47% of patients had kidney problems in varying stages. The range and median (IQR) of the length of hospital stay were 3-90 days and 13 (9-16) days, respectively. Four patients (13%) also died.

The range and mean (SD) of uNGAL level at admission in all patients was 46.1 to 172.5 ng/mL and 89.94 ± 30.9 ng/mL, respectively, which showed no significant differences between the two sexes, between living and deceased patients, and between patients with and without a history of cardiac disease. Although the mean uNGAL level in patients in risk and injury stages of the RIFLE criteria was higher than normal patients; however, the difference between them was not significant (Table 3). The increase in uNGAL was directly related to the increase in SOFA score (Spearman's rho=0.360, $P=0.043$). Furthermore uNGAL changes was not significantly related to age

Table 1. Patients characteristics

Variable	
Age (y), Mean ± SD	63 ± 17
Gender, No. (%)	
Male	18 (56)
Female	14 (44)
Cause of ICU admission, No. (%)	
After heart surgery	21 (66)
Internal problems	4 (13)
Trauma	3 (9)
After general surgery	2 (6)
Infectious disease	1 (3)
Neurological problems	1 (3)
Disease history, No. (%)	
Dialysis	0 (0)
Nephrotic syndrome	5 (16)
Cardiovascular disease	24 (75)
SOFA score, Median (IQR)	2.5 (2-4)

IQR: Interquartile range, SOFA: Sequential Organ Failure Assessment.

Table 2. Kidney status of patients at the time of admission to the ICU and during the hospital stay

Variable	
Creatinine at admission (mg/dL), Mean ± SD	0.83 ± 0.12
The first increased creatinine (md/dL), Mean ± SD	1.33 ± 0.49
Increased creatinine ratio to creatinine at admission, median (IQR)	1.44 (1.38-1.6)
Creatinine rise day, No. (%)	
Third day or less	13 (41%)
Fourth to seventh days	15 (47%)
Eighth day onwards	4 (12%)
RIFLE criteria, No. (%)	
None	17 (53%)
Risk	12 (38%)
Injury	2 (6%)
Failure	1 (3%)

IQR: Interquartile range; RIFLE criteria: Risk, Injury, Failure, Loss, and End-stage Kidney.

Table 3. Comparison of uNGAL levels at ICU admission between patient characteristics

Variable	Mean (SD)	*P* value
Gender		
Man	93.3 ± 34.7	0.499*
Female	85.7 ± 25.9	
History of heart disease		
Yes	83.0 ± 29.5	0.126*
No	93.9 ± 26.5	
Patient outcome		
Alive	88.0 ± 32.1	0.368*
Deceased	103.2 ± 17.7	
RIFLE criteria		
None	75.7 ± 6.0	0.674**
Risk	86.4 ± 24.5	
Injury	93.9 ± 37.2	

uNGAL: urinary neutrophil gelatinase-dependent lipocalin; RIFLE criteria: Risk, Injury, Failure, Loss, and End-stage Kidney; ICU: intensive care unit.
* Independent sample *t* test, ** One-way ANOVA.

or creatinine elevation ratio (Pearson's correlation coefficient=0.029 *P*=0.874 and Spearman's rho=0.178, *P*=0.330, respectively).

Discussion

The findings of our study showed that the first-day uNGAL level was not helpful in predicting renal impairment based on the RIFLE criteria in ICU admitted patients. Although the increase in uNGAL was directly related to the SOFA score, it was not significantly related to the increase in creatinine ratio.

The incidence of AKI has increased, especially in patients admitted to the ICU (17), For early AKI diagnosis and classification in patients admitted to the ICU, in addition to urine output and serum creatinine, several biomarkers have been studied so far, of which NGAL seems to be more studied than others (14). However, despite the great heterogeneity of AKI, it is not surprising that NGAL level can predict AKI well in a particular population of patients while not very effective in other populations (18). For example, Dobilien et al reported that uNGAL was a good marker for predicting AKI in infants and children admitted to the ICU (19). In contrast, Albeladi and Algethamy reported that although uNGAL level of the first and second day was the predictor of the requirement to renal replacement therapy in adult patients admitted to the ICU, it is less accurate in early detection of AKI and its severity (20). However, McMahon et al did not find the statistical and clinical usefulness of the addition of uNGAL to the AKI predictive model in ICU patients in contrast to simpler models (15). On the other hand, Albert et al, in a meta-analysis in 2020, reported that plasma and urinary NGAL were able to identify patients at risk for AKI, but determining the appropriate cut-off point needed further investigation (21).

Our study also showed that in patients in the ICU, uNGAL level could not predict the onset and severity of AKI based on RIFLE criteria. Heterogeneity of patients, the effect of other factors such as disease severity, infection and inflammation on the level of NGAL (22), heterogeneity of AKI nature and different definitions of AKI, as well as non-standardization of NGAL assay kits (23) can be the reasons for inconsistency in the results of different studies. Therefore, due to the controversial results of studies on biomarkers predicting AKI, at present, it is not possible to introduce a single biomarker for clinical use, and more extensive studies are needed in this regard (14).

Conclusion

The findings of our study showed that, in patients admitted to the ICU, first-day uNGAL level was not helpful in predicting AKI based on the RIFLE criteria.

Limitations of the study

Due to the high cost of uNGAL laboratory kits, the sample size of the present study was considered low. Therefore, it may not be possible to generalize the results to all patients.

Authors' contribution

NR, and SJ were the principal investigators of the study. All authors were included in preparing the concept and design. SH and NR revisited the manuscript and critically evaluated the intellectual contents. All authors participated in preparing the final draft of the manuscript, revised the manuscript and critically evaluated the intellectual contents. All authors have read and approved the content of the manuscript and confirmed the accuracy or integrity of any part of the work.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

The study was approved by the ethics committee of Qazvin University of Medical Sciences (IR.QUMS.REC.1397.104). Besides, ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

Funding/Support

This work was supported by Qazvin University of Medical Sciences (Contract no. 28/32/47206, Date: March 21, 2018).

References

1. Koeze J, Keus F, Dieperink W, van der Horst ICC, Zijlstra JG, van Meurs M. Incidence, timing and outcome of AKI in critically ill patients varies with the definition used and the addition of urine output criteria. BMC Nephrol. 2017;18:70. doi: 10.1186/s12882-017-0487-8.
2. Khwaja A. KDIGO clinical practice guidelines for acute kidney injury. Nephron Clin Pract. 2012;120:c179-84. doi: 10.1159/000339789.
3. Hoste EAJ, Clermont G, Kersten A, Venkataraman R, Angus DC, De Bacquer D, et al. RIFLE criteria for acute kidney injury are associated with hospital mortality in critically ill patients: a cohort analysis. Crit Care. 2006;10:R73-R. doi: 10.1186/cc4915.
4. Levey AS, Eckardt K-U, Tsukamoto Y, Levin A, Coresh J, Rossert J, et al. Definition and classification of chronic kidney disease: A position statement from Kidney Disease: Improving Global Outcomes (KDIGO). Kidney Int. 2005;67:2089-100. doi: 10.1111/j.1523-1755.2005.00365.x.
5. Nisula S, Kaukonen K-M, Vaara ST, Korhonen A-M, Poukkanen M, Karlsson S, et al. Incidence, risk factors and 90-day mortality of patients with acute kidney injury in Finnish intensive care units: the FINNAKI study. Intensive Care Med. 2013;39:420-8. doi: 10.1007/s00134-012-2796-5.
6. Stevens LA, Levey AS. Measured GFR as a Confirmatory Test for Estimated GFR. J Am Soc Nephrol. 2009;20:2305-13. doi: 10.1681/ASN.2009020171.
7. Göcze I, Jauch D, Götz M, Kennedy P, Jung B, Zeman F, et al. Biomarker-guided Intervention to Prevent Acute Kidney Injury After Major Surgery: The Prospective Randomized BigpAK Study. Ann Surg. 2018;267:1013-20. doi: 10.1097/SLA.0000000000002485.
8. Peres LAB, Cunha Júnior ADd, Schäfer AJ, Silva ALd, Gaspar AD, Scarpari DF, et al. Biomarkers of acute kidney injury. J Bras Nefrol. 2013;35:229-36. doi: 10.5935/0101-2800.20130036.
9. Vanmassenhove J, Vanholder R, Nagler E, Van Biesen W. Urinary and serum biomarkers for the diagnosis of acute kidney injury: an in-depth review of the literature. Nephrol Dial Transplant. 2013;28:254-73. doi: 10.1093/ndt/gfs380.
10. Tuladhar SM, Püntmann VO, Soni M, Punjabi PP, Bogle RG. Rapid Detection of Acute Kidney Injury by Plasma and Urinary Neutrophil Gelatinase-associated Lipocalin After Cardiopulmonary Bypass. J Cardiovasc Pharmacol. 2009;53:261-6. doi: 10.1097/FJC.0b013e31819d6139.
11. Haase M, Bellomo R, Haase-Fielitz A. Neutrophil gelatinase-associated lipocalin. Curr Opin Crit Care. 2010;16:526-32. doi: 10.1097/MCC.0b013e328340063b.
12. Gan J, Zhou X. Comparison of urine neutrophil gelatinase-associated lipocalin and interleukin-18 in prediction of acute kidney injury in adults. Medicine (Baltimore). 2018;97:e12570. doi: 10.1097/md.0000000000012570.
13. Parikh A, Rizzo JA, Canetta P, Forster C, Sise M, Maarouf O, et al. Does NGAL reduce costs? A cost analysis of urine NGAL (uNGAL) & serum creatinine (sCr) for acute kidney injury (AKI) diagnosis. PLoS One. 2017;12:e0178091. doi: 10.1371/journal.pone.0178091.
14. Amaral Pedroso L, Nobre V, Dias Carneiro de Almeida C, da Silva Praxedes MF, Sernizon Guimarães N, Simões ESAC, et al. Acute kidney injury biomarkers in the critically ill. Clin Chim Acta. 2020;508:170-8. doi: 10.1016/j.cca.2020.05.024.
15. McMahon BA, Galligan M, Redahan L, Martin T, Meaney E, Cotter EJ, et al. Biomarker Predictors of Adverse Acute Kidney Injury Outcomes in Critically Ill Patients: The Dublin Acute Biomarker Group Evaluation Study. Am J Nephrol. 2019;50:19-28. doi: 10.1159/000500231.
16. Koeze J, van der Horst IC, Keus F, Wiersema R, Dieperink W, Kootstra-Ros JE, et al. Plasma neutrophil gelatinase-associated lipocalin at intensive care unit admission as a predictor of acute kidney injury progression. Clin Kidney J. 2020;13:994-1002. doi: 10.1093/ckj/sfaa002.
17. Vanmassenhove J, Veys N, Van Biesen W. Prevention and conservative management of acute kidney injury. Minerva Urol Nefrol. 2016;68:58-71.
18. Griffin BR, Gist KM, Faubel S. Current Status of Novel Biomarkers for the Diagnosis of Acute Kidney Injury: A Historical Perspective. J Intensive Care Med. 2020;35:415-24. doi: 10.1177/0885066618824531.
19. Dobilienė D, Masalskienė J, Rudaitis Š, Vitkauskienė A, Pečiulytė J, Kėvalas R. Early Diagnosis and Prognostic Value of Acute Kidney Injury in Critically Ill Patients. Medicina

(Kaunas). 2019;55:506. doi: 10.3390/medicina55080506.
20. Albeladi FI, Algethamy HM. Urinary Neutrophil Gelatinase-Associated Lipocalin as a Predictor of Acute Kidney Injury, Severe Kidney Injury, and the Need for Renal Replacement Therapy in the Intensive Care Unit. Nephron Extra. 2017;7:62-77. doi: 10.1159/000477469.
21. Albert C, Zapf A, Haase M, Röver C, Pickering JW, Albert A, et al. Neutrophil Gelatinase-Associated Lipocalin Measured on Clinical Laboratory Platforms for the Prediction of Acute Kidney Injury and the Associated Need for Dialysis Therapy: A Systematic Review and Meta-analysis. Am J Kidney Dis. 2020;76:826-41.e1. doi: 10.1053/j.ajkd.2020.05.015.
22. Vanmassenhove J, Glorieux G, Lameire N, Hoste E, Dhondt A, Vanholder R, et al. Influence of severity of illness on neutrophil gelatinase-associated lipocalin performance as a marker of acute kidney injury: a prospective cohort study of patients with sepsis. BMC Nephrol. 2015;16:18. doi: 10.1186/s12882-015-0003-y.
23. Kift RL, Messenger MP, Wind TC, Hepburn S, Wilson M, Thompson D, et al. A comparison of the analytical performance of five commercially available assays for neutrophil gelatinase-associated lipocalin using urine. Ann Clin Biochem. 2013;50:236-44. doi: 10.1258/acb.2012.012117.

Copyright © 2022 The Author(s); Published by Nickan Research Institute. This is an open-access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.