Urinary Neutrophil Gelatinase-associated Lipocalin as a Biomarker of Kidney Injury in Hematologic-Oncologic Patients Receiving Amphotericin B

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Introduction. The aim of the present study was to compare the changing pattern of urine neutrophil gelatinase-associated lipocalin (NGAL) with serum as well as urine creatinine during amphotericin B treatment and determine its accuracy in the early detection of amphotericin B nephrotoxicity.

Materials and Methods. A cohort study was performed during 9 months at 3 hematology-oncology services. Patients aged 15 years and greater with no documented history of acute kidney injury or chronic kidney disease, planned to receive any formulation of amphotericin B for at least 1 week, were included. Serum as well as urine creatinine and urine NGAL were determined on days zero, 3, 5, 7, 10, and 14 of amphotericin B treatment.

Results. Forty patients with the mean age of 38.0 ± 14.1 years were recruited. Eleven of 40 patients (27.5%) developed amphotericin B nephrotoxicity. The overall changes in the mean values of urine NGAL were not significant during amphotericin B treatment, neither within nor between the two groups. The area under the curve of urine NGAL (0.7; 95% confidence interval, 0.59 to 0.96) on day zero was significantly higher than that of serum creatinine (0.46; 95% confidence interval, 0.27 to 0.66; P = .01) for predicting amphotericin B nephrotoxicity.

Conclusions. The incremental pattern of urine NGAL during amphotericin B treatment was not significant compared to baseline values. The urine level of NGAL on the first day of amphotericin B administration was more accurate than serum creatinine in predicting acute kidney injury caused by this agent.

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INTRODUCTION

Serum creatinine is the product of a nonenzymatic hydrolysis of endogenous creatine in the skeletal muscles and liver.[1] It has been considered as a classic marker of kidney function. However, serum creatinine has several drawbacks in clinical practice. First, many nonrenal factors such as age, sex, race, protein intake, muscle mass, medications, infections, and inflammatory status may potentially alter its level.[2] Second, serum creatinine and glomerular filtration rate (GFR) are hyperbolically, rather than linearly, related. In this regards, an increase in serum creatinine from 4 mg/dL to 8 mg/dL produces the same proportional decrease of GFR, as it increases from 1 mg/dL to 2 mg/dL.[3] Third, serum creatinine can overestimate kidney function especially in the early phase (24 to 48 hours) of acute kidney injury (AKI). This can lead

to delay in the diagnosis of kidney injury as well as inappropriate dosing of medications with renal route of elimination.[2, 3]

Considering the limitations of serum creatinine, and on the other hand, being cumbersome, costly, and not readily available direct measurement methods of GFR (eg, urinary inulin clearance and the plasma 99mTc-diethylenetriaminepentaacetic acid),[3] several new markers of kidney injury has been investigated during the recent 2 decades. Neutrophil gelatinase-associated lipocalin (NGAL), a 25-kDa protein with 178 amino acids belonging to the lipocalin superfamily, is a prominent example in this regard. Its expression is induced in response to kidney injury, and it involves in maintaining cell homeostasis by modulating the transport of hydrophilic substances through the membrane.[4] Although serum as well as urine NGAL are among the most extensively evaluated novel AKI biomarkers in different clinical settings such as cardiopulmonary bypass and diabetic nephropathy, its role in the detection of AKI caused by medications is largely limited to radiocontrast agents and cisplatin.[5]

Nephrotoxicity is the most clinically significant adverse reaction of amphotericin B.[6] Early diagnosis of amphotericin B nephrotoxicity is essential for optimal management and preventing its clinical as well as economical complications.[7] In most experimental and clinical studies on amphotericin B nephrotoxicity, serum creatinine has been used as a marker of kidney function. Therefore, the 2012 Kidney Disease: Improving Global Outcomes guideline has emphasized on investigating novel biomarkers of kidney function in this setting.[8] To our knowledge, only 3 experimental and 3 clinical studies published to date have explored other biomarkers of kidney injury rather than serum creatinine, including alkaline phosphatase, g-glutamyltransferase, lactate dehydrogenase, N-acetyl-b-D-glucosaminidase, a-glutathione S-transferase, p-glutathione S-transferase, b-glucuronidase, serum as well as urine cystatin C, and urine kidney injury molecule 1 (KIM-1).[9-14]

The aim of the present study was to compare the changing pattern of urine NGAL with serum creatinine during amphotericin B treatment and also their accuracy in the early detection of amphotericin B nephrotoxicity in patients hospitalized at hematology-oncology services.

MATERIALS AND METHODS

Within 9 months from August 2015 to April 2016, a cohort study was performed at 2 hematology-oncology and one hematopoietic stem cell transplantation services of Namazi Hospital, affiliated to Shiraz University of Medical Sciences, Shiraz, Iran. The medical ethics committee of the hospital approved the study protocol and a written informed consent form was taken from all patients.

Patients aged equal or greater than 15 years, without documented history of AKI and chronic kidney disease, without documented history of receiving amphotericin B by any administration route within the recent 14 days, and planned to receive any formulation of amphotericin B intravenously for at least 1 week were considered eligible for inclusion. Acute kidney injury was defined by an increase in serum creatinine of 0.3 mg/dL and greater within 48 hours, an increase in serum creatinine by at least 1.5 times baseline within the prior 7 days, or urine volume less than 0.5 mL/kg/h for 6 hours.[8] Chronic kidney disease was considered when there was a clearance creatinine below 60 mL/min/1.73 m^2 calculated by the simplified Modification of Diet in Renal Disease equation or documented history of regular peritoneal or hemodialysis for more than 3 months.[15]

During the course of amphotericin B treatment, serum creatinine was monitored daily. Since most cases of amphotericin B nephrotoxicity have been reported during the first 2 weeks of treatment,[16,17] urine samples for the determination of creatinine and NGAL were collected at certain time points including days zero, 3, 5, 7, 10, and 14 of amphotericin B treatment. Urine samples were frozen at -80°C until completing the sampling of all recruited patients. Measurement of serum as well as urine creatinine was done by an auto-analyzer (Shanghai Xunda Medical Instrument, China) via exploiting a modified Jaffe colorimetric reaction. Urine level of NGAL was determined by the double sandwich enzyme-linked immunosorbent assay technique (Bioassay Technology Laboratory, Shanghai, China). Briefly, urine samples were centrifuged at 2000 rpm to 3000 rpm for 20 minutes. Then, 40 µL of the supernatant along with 10 µL of anti-NGAL antibody and 50 µL of streptavidin-horseradish peroxidase conjugate were transferred to each well. The wells were gently shaken for 60 minutes at 37°C. After that, at least 0.35 mL of

diluted washing solution with distilled water at a 1:30 ratio was added to each well and retained for 30 seconds. This phase was repeated 5 times. Then, 50 µL of chromogen solution A and 50 µL of chromogen solution B were added to each well and the mixture was incubated for 10 minutes at 37°C, while protecting wells from light. Finally, 50 µL of stop solution was added to each well, and within 10 minutes after addition of the stop solution, light absorption of the admixture was determined at 450 nm wavelength by the enzyme-linked immunosorbent assay reader.

A decrease in estimated GFR by 50% and larger, calculated by the Cockcroft-Gault formula, or an increase in serum creatinine (doubling from the baseline value) was considered as amphotericin B nephrotoxicity.[18]

Continuous data were expressed as mean ± standard deviation. Categorical variables were reported as percentages. Comparison of the mean values of studied biomarkers (serum creatinine and urine NGAL) at certain time points during amphotericin B treatment (days zero, 3, 5, 7, 10, and 14) within and between patients with and without amphotericin B nephrotoxicity was done by the 1-way analysis of variance with repeated measures. The accuracy of serum creatinine and urine NGAL at days zero, 3, 5, 7, 10, and 14 of treatment in predicting or detecting amphotericin B nephrotoxicity was evaluated by the receiver operating characteristic curves of sensitivity and specificity and relevant data were expressed as area under the curve (AUC) and 95% confidence intervals (CI). *P* values less than .05 were considered significance. All the above statistical analyses were performed using the SPSS software (Statistical Package for the Social Sciences, version 20.0, IBM Corp, New York, NY, USA).

RESULTS

Ninety patients were planned to receive amphotericin B during the study period. Among these, 50 patients did not meet the inclusion criteria because of switching to other antifungal agents including voriconazole and posaconazole (n = 10), receiving amphotericin B for less than 1 week (n = 18), death before 1 week of amphotericin B treatment (n = 7), receiving amphotericin B during the recent 2 weeks (n = 5), age below 18 years (n = 3), and tolerating amphotericin B for only 2 days (n = 2). Finally, 40 individuals were recruited into study.

The mean age of the cohort was 38.0 ± 14.1 years. Twenty six (65%) individuals were men. Liposomal and conventional amphotericin B were given to 25 (62.5%) and 15 (37.5%) patients, respectively. Eleven of 40 (27.5%) patients developed amphotericin B nephrotoxicity during the treatment course.

Figure 1 demonstrates the changing trend in the mean value of serum creatinine and urine NGAL at the studied time points during amphotericin B treatment. The overall incremental trend seen with serum creatinine was significant in patients with and without amphotericin B nephrotoxicity (*P* = .04).

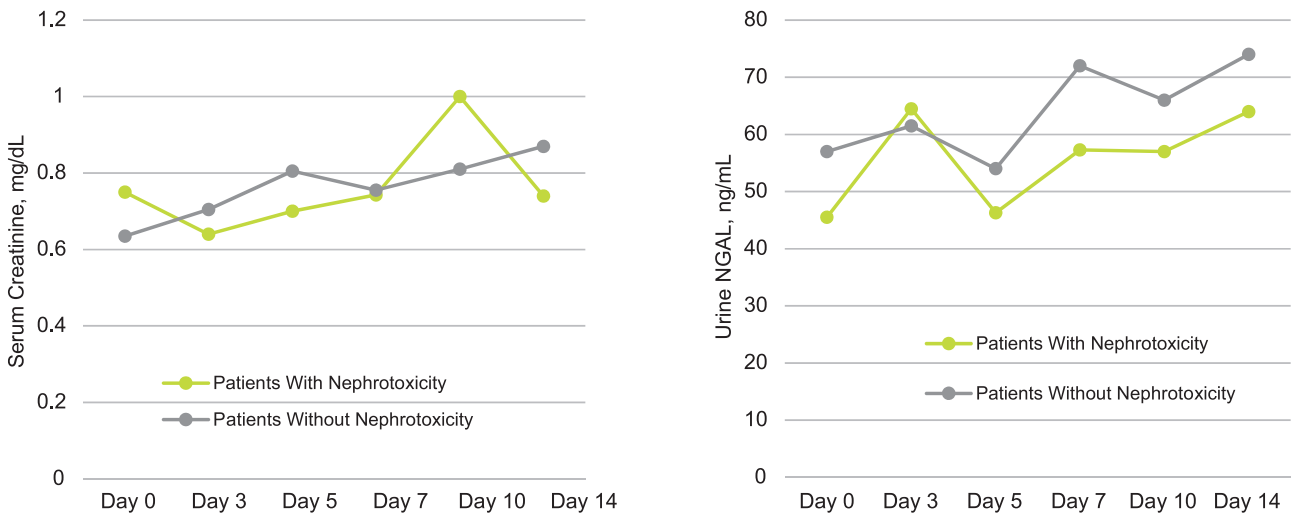

Figure 1. The changing pattern of serum creatinine and urine neutrophil gelatinase-associated lipocalin (NGAL) at studied time points during the course of amphotericin B treatment in patients with and without amphotericin B nephrotoxicity.

In contrast, the difference in mean values of serum creatinine between the two groups during the course of amphotericin B treatment did not reach the level significance (P = .98). In contrast, the overall changes in the mean values of urine NGAL were not significant neither within (P = .25) nor between (P = .55) the two groups during amphotericin B treatment. Considering each 2 studied time intervals during amphotericin B treatment (Tables 1 and 2), the mean changes in serum creatinine and urine NGAL values were comparable between the patients with and without amphotericin B nephrotoxicity.

Analysis of the receiver operating characteristics curves of sensitivity and specificity demonstrated the AUC of urine NGAL (0.765; 95% CI, 0.588 to 0.962) on day zero was significantly higher than that of serum creatinine (0.464; 95% CI, 0.268 to 0.660; P = .01) for predicting amphotericin B nephrotoxicity. In contrast, these values were comparable at the remaining studied time points including days 3, 5, 7, and 10 (Table 3 and Figure 2). Considering the fact that urine samples of only 11 patients were available for determining urine NGAL at day 14 of amphotericin B treatment, calculating AUC values was not feasible at this time point.

DISCUSSION

The changing pattern of urine NGAL was incremental during the course of amphotericin B treatment in both patients with and without amphotericin B nephrotoxicity in our cohort. However, these alterations did not reach the level of significance. Three major issues can be taken into account for this finding. First, limited measurements of urine NGAL (6 times) may not reflect its real changing pattern in amphotericin B recipients. The relatively small sample size of the study highlights this issue. Second, although most episodes of amphotericin B nephrotoxicity have been reported to occur during the first 14 days of amphotericin B treatment, but the duration of patients follow-up and sampling (2 weeks)

Table 1. Mean Changes of Serum Creatinine Values at Studied Time Points During Amphotericin B Treatment Between Patients With and Without Amphotericin B Nephrotoxicity

Index Time Point	Mean Changes in Serum Creatinine (95% Confidence Interval), mg/dL				
	Day 3	Day 5	Day 7	Day 10	Day 14
Day 0	0.02 (-0.19 to 0.23)	-0.06 (-0.41 to 0.30)	-0.06 (-0.28 to 0.16)	-0.21 (-0.48 to 0.06)	-0.12 (-0.42 to 0.19)
Day 3	...	-0.08 (-0.37 to 0.22)	-0.08 (-0.31 to 0.15)	-0.23 (-0.56 to 0.10)	-0.14 (-0.37 to 0.10)
Day 5	...	...	-0.01 (-0.24 to 0.23)	-0.16 (-0.48 to 0.17)	-0.06 (-0.45 to 0.33)
Day 7	...	...	...	-0.15 (-0.35 to 0.05)	-0.06 (-0.35 to 0.24)
Day 10	...	...	...	...	0.10 (-0.17 to 0.36)

Table 2. Mean Changes of Urine Neutrophil Gelatinase-associated Lipocalin (NGAL) Values at Studied Time Points During Amphotericin B Treatment Between Patients With and Without Amphotericin B Nephrotoxicity

Index Time Point	Mean Changes in Urine NGAL (95% Confidence Interval), ng/mL				
	Day 3	Day 5	Day 7	Day 10	Day 14
Day 0	-11.58 (-39.93 to 16.78)	-1.84 (-32.48 to 28.80)	-13.64 (-54.29 to 27.01)	-10.71 (-55.59 to 34.18)	-17.86 (-51.13 to 15.40)
Day 3	...	9.73 (-20.14 to 39.61)	-2.07 (-43.52 to 39.39)	0.87 (-43.33 to 45.07)	-6.30 (-50.97 to 38.40)
Day 5	...	...	-11.80 (-31.47 to 7.87)	-8.87 (-37.53 to 19.80)	-16.02 (-42.10 to 10.05)
Day 7	...	...	...	2.93 (-30.37 to 36.24)	-4.22 (-33.54 to 25.10)
Day 10	...	...	...	...	-7.16 (-36.54 to 22.23)

Table 3. Area Under the Curve of Serum Creatinine and Urine Neutrophil Gelatinase-associated Lipocalin (NGAL) at Studied Time Points of Amphotericin B Treatment for Predicting Amphotericin B Nephrotoxicity

Time Point	Serum Creatinine		Urine NGAL	
	Area Under Curve (95% Confidence Interval)	*P*	Area Under Curve (95% Confidence Interval)	*P*
Day 0	0.45 (0.25 to 0.64)	.60	0.77 (0.57 to 0.96)	.01
Day 3	0.37 (0.18 to 0.56)	.21	0.64 (0.47 to 0.81)	.17
Day 5	0.40 (0.20 to 0.60)	.32	0.63 (0.44 to 0.82)	.21
Day 7	0.49 (0.28 to 0.71)	.94	0.51 (0.32 to 0.69)	.95
Day 10	0.52 (0.22 to 0.82)	.89	0.65 (0.40 to 0.90)	.29

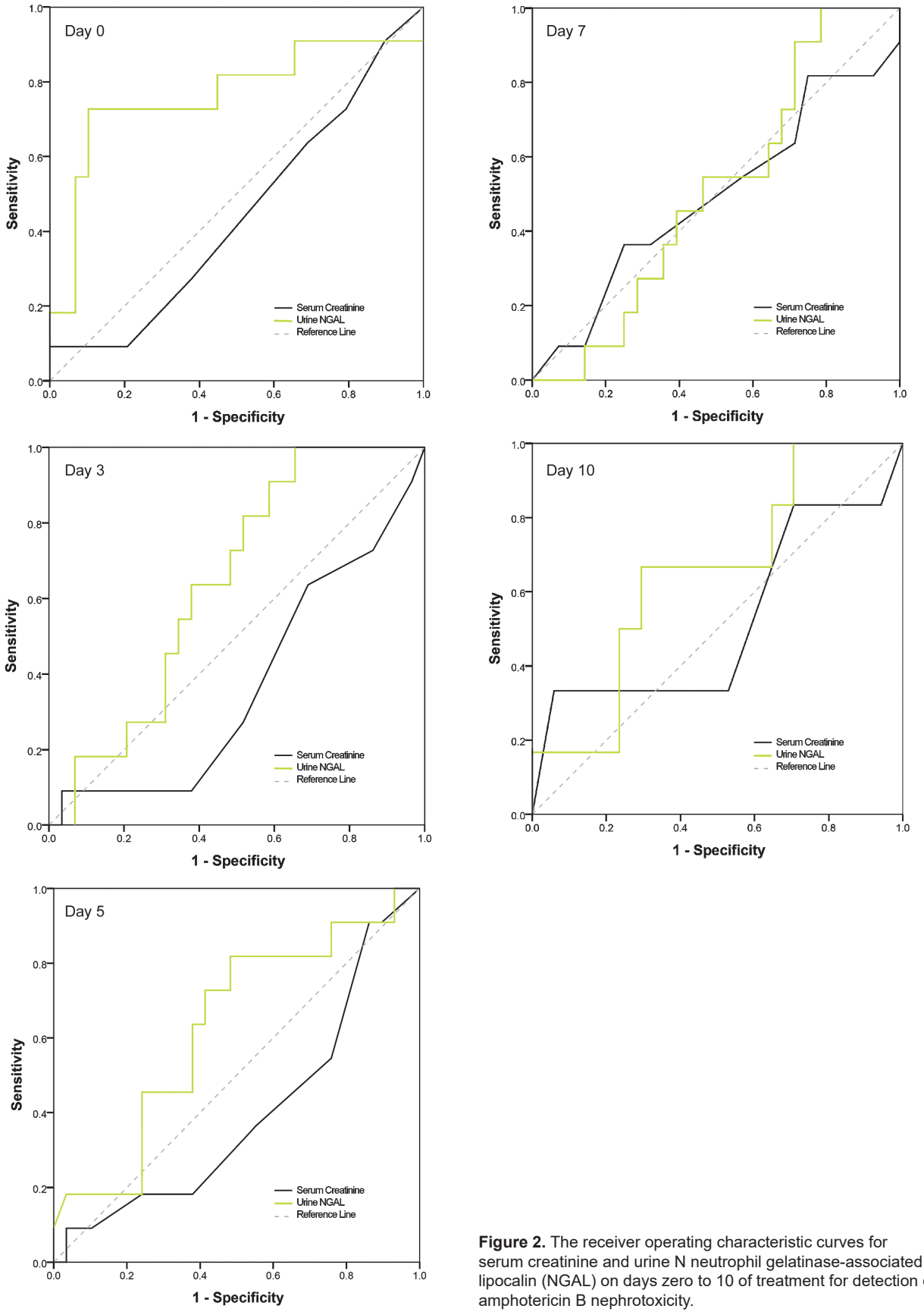

Figure 2. The receiver operating characteristic curves for serum creatinine and urine N neutrophil gelatinase-associated lipocalin (NGAL) on days zero to 10 of treatment for detection of amphotericin B nephrotoxicity.

may be insufficient for detecting all plausible amphotericin B nephrotoxicity events. In this regard, approximately 6 hours after a kidney injury, urine NGAL increases rapidly due to an upregulated expression and secretion in different sites of the tubule.[19,20] Last but not least, gene expression and transgenic animal studies have implicated that an upregulation of NGAL occurs mostly in the distal nephron segments including the thick ascending limb of Henle and the collecting ducts. However, the proximal tubule is the most common site of the injury in AKI caused by most medications including amphotericin B.[4] Considering this issue, and on the other hand, amphotericin B also exploits its nephrotoxic effects through decreasing GFR,[6] concurrent measurement of NGAL in serum can be beneficial to assess the whole aspect of amphotericin B nephrotoxicity.

In accordance with our findings, Shinke and colleagues demonstrated that among studied renal biomarkers including KIM-1, monocyte chemotactic protein-1, N-acetyl-b-D-glucosaminidase, and β2-microglobulin in lung cancer patients that received cisplatin, urine NGAL-creatinine ratio did not differ significantly between patients with and without AKI.[21] This was in contrast to findings of at least 3 other similar clinical studies in the setting of cisplatin-induced AKI.[22-24] The authors justified this discrepancy by the difference in time points of sampling and measuring urine NGAL with regard to cisplatin infusion and also variations in diagnostic criteria for defining AKI.[21] In a double-blinded placebo-controlled trial on possible nephroprotective effects of silymarin on cisplatin nephrotoxicity, Shahbazi and coworkers also reported that urine NGAL-urine creatinine ratio increased significantly after cisplatin infusion.[25] In a preliminary clinical study about the effect of ascorbic acid on colistin-associated nephrotoxicity, urinary excretion of NGAL during and at the end of colistin treatment was significantly higher than baseline values.[26] Similar findings were observed in the setting of contrast-induced nephropathy.[27] In brief, urine NGAL has increased significantly during the course of treatment with studied nephrotoxic agents in most clinical investigations published so far.

With regard to the sensitivity and specificity, urine NGAL only at the initiating day of amphotericin B treatment, rather than other studied time points, was more accurate compared to serum and urine creatinine in predicting amphotericin B nephrotoxicity in our population. Shinke and colleagues reported that urinary KIM-1 or MCP-1 had significantly higher accuracy than urinary NGAL in detecting AKI in patients received cisplatin.[21] In contrast, at least 1 investigation demonstrated that urine NGAL predicts contrast-induced nephropathy 24 hours before serum creatinine in patients undergoing coronary angiography.[28] The performance of urine as well as serum NGAL in the prediction of AKI has been demonstrated in several clinical studies especially in the pediatric population.[4] For example, Hirsch and colleagues reported that serum and urine NGAL significantly increased within 2 hours of contrast agent administration in children who developed contrast nephropathy than the control group. The 2-hour NGAL concentrations in the urine ($P < .001$) and plasma ($P < .001$) were identified as independent predictors of contrast-induced nephropathy.[29] Similarly, in at least 2 studies in adult patients, an early increase in both urine and plasma NGAL has been documented within 4 and 2 hours after the administration of contrast media agents.[30,31] Other relevant clinical studies on renal biomarkers of amphotericin B generally have not considered this issue. In a clinical trial investigating oral N-acetylcysteine for preventing amphotericin B-induced nephrotoxicity, serum and urine cystatin C and urine KIM-1 at days zero, 7, and 14 of amphotericin B treatment had nonsignificant comparable accuracy compared to serum and urine creatinine in detecting amphotericin B nephrotoxicity.[14] Relatively small sample size, limited times of measuring urine NGAL, and lack of a gold standard method such as an exogenous agent (eg, inulin, radiolabeled or nonradiolabeled contrast media) for calculating GFR and determining nephrotoxicity can partially justify our findings. However, it is noteworthy that an increase in serum creatinine level or a decrease in estimated GFR exploited by us is the most commonly used definition of amphotericin B nephrotoxicity in the literature.[18]

To reduce the possibility of laboratory variations in the measurement of urinary renal biomarkers, determination was conducted on samples frozen at -80°C for up to 9 months. Therefore, degradation of renal biomarkers, especially NGAL, during

the storage period can be a potential concern. In this regards, Nauta and coworkers demonstrated that storage of urine at either -20°C or -80°C was associated with both a gradual decrease in the concentration and also an increase in the variability of most studied markers including NGAL. Accordingly, the authors recommended measurement of renal biomarkers in fresh urine samples and interpreting with caution the results of studies measuring these indexes in frozen urine samples.[32] In contrast, another study reported that if urine samples were immediately cooled to 4°C and subsequently frozen at -80°C within 2 days, both KIM-1 and NGAL levels in the urine were stable for at least 6 months.[33] The package insert of the enzyme-linked immunosorbent assay kit used in our study declares that NGAL in urine samples is stable for 12 months at -20°C. Overall, it seems unlikely that the storage condition (up to 9 months at -80°C) can significantly alter NGAL level in urine samples and affect our results.

As noted above, relatively small sample size (lack of statistical power due to type II error), limited frequency of urine sampling, insufficient follow-up period, lack of a gold standard method to determine GFR, no concurrent measurement of NGAL in serum, and sample storage duration as well as condition of urine samples can be considered as the major drawbacks of our study. Implementing various inclusion criteria for recruiting patients into the study and lack of any formulation of amphotericin B in Iran's pharmaceutical market for a period during the study can partially explain our relatively small sample size. In contrast, investigating urine NGAL for assessing amphotericin B nephrotoxicity in clinical setting for the first time to best of our knowledge can be considered as the strength of our survey.

CONCLUSIONS

Our data suggests that urine NGAL increased during the course of amphotericin B treatment for any indication in patients with hematologic-oncologic diseases. However, the changing pattern in its mean level was not significant compared to baseline values and also was comparable between patients with and without amphotericin B nephrotoxicity. The urine level of NGAL on the first day of amphotericin B administration was more accurate than serum creatinine in the early prediction of amphotericin B-induced AKI. To elucidate the real role of NGAL in diagnosis and assessment of amphotericin B nephrotoxicity, urine sampling at more frequent and close time points in a larger population, along with concurrent measurement of NGAL in serum, and exploiting a gold standard method of kidney function calculation seem necessary. Before that, the clinical application of urine NGAL for the routine assessment of AKI caused by different nephrotoxic medications such as amphotericin B seems to be premature and irrational.

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CONFLICT OF INTEREST

None declared.

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