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Urinary and Serum Biomarkers for Prediction of Acute Kidney Injury in Patients Undergoing Liver Transplantation

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

EF Lidia Lewandowska
EF Jolanta Małyszko
AEF Joanna Matuszkiewicz-Rowińska

Department of Nephrology, Dialysotherapy, and Internal Medicine, Medical University of Warsaw, Warsaw, Poland

Corresponding Author: Joanna Matuszkiewicz-Rowińska, e-mail: jrowinska@gmail.com
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Acute kidney injury (AKI) is a frequent and serious complication of orthotopic liver transplantation (OLT), with a significant impact on mortality, graft survival, and chronic kidney disease. Currently, the diagnosis of AKI is based on changes in serum creatinine, which is a late marker, usually rising when there is already significant damage to the renal parenchyma. During the last 2 decades, various biomarkers have been studied in many clinical situations, mostly after cardiac surgery, in drug-induced AKI, or in sepsis. The present article summarizes the data on those biomarkers that have been evaluated for the prediction of AKI in patients undergoing OLT.

MeSH Keywords: Acute Kidney Injury • Biological Markers • Liver Transplantation

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Background

Acute kidney injury (AKI) is a serious complication of orthotopic liver transplantation (OLT). The frequency of its occurrence ranges broadly from 6% to 90% depending on various factors, diagnostic criteria applied, presence of post-reperfusion syndrome, and differences between studied populations [1–5]. About 15–30% of those patients require renal replacement therapy (RRT) immediately after surgery [6,7]. The etiology of post-transplant AKI is multifactorial, constituting a combination of various factors: the recipient-, graft-, and surgery-related events, with preoperative renal dysfunction and hepatic ischemia-reperfusion injury usually playing crucial roles.

Numerous studies demonstrated that development of AKI is associated with increased mortality and poor graft survival, as well as high risk of development of chronic renal disease [1,2,4,7–9]. Need for RRT is associated with a very high mortality, reaching up to 50% within 90 days from transplantation [10,11]. AKI also leads to prolonged hospitalization and significant increase in hospitalization costs and ICU readmissions, and is the major risk factor for cardiac events [1,9,12,13]. Thus, early diagnosis and damage minimization are crucial.

Currently, AKI is diagnosed based on the RIFLE/AKIN criteria, usually with KDIGO (Kidney Disease: Improving Global Outcomes) modification [14]. This classification has been developed by international societies to ensure uniformity of the definition of AKI. The diagnosis of AKI is based on absolute increase in serum creatinine concentration by >0.3 mg/dL from baseline during 48 h or an increase by >50%. Taking into account even such small changes in serum creatinine is supposed to allow earlier diagnosis of AKI. Urine volume is another diagnostic criterion in KDIGO classification, although it is rarely used. All 3 classifications – RIFLE, AKIN, and KDIGO – are presented in Table 1. They differ with regard to the creatinine concentration criteria, while urine volume criteria are the same.

However, serum creatinine is not a good parameter of renal injury, especially among patients with liver failure. It is affected by numerous extrarenal factors, such as age, sex, muscle mass, dietary protein and creatine intake, hydration status, or ingestion of drugs excreted through the proximal tubule. Synthesis of creatinine from creatine is significantly impaired (by up to 50%) in patients with liver cirrhosis, who present with signs of protein deficiency, muscle atrophy, edema, and increased tubular creatinine excretion [15]. Moreover, in some creatinine assays (those performed using Jaffe's reaction), interference with serum bilirubin may lead to overestimation of renal function. But above all, it is a late marker – its level usually rises after several hours from the injury (ischemic, toxic), when there is already significant damage to the renal parenchyma. Moreover, fluid overload and need for massive fluid transfusions can mask the increase in serum creatinine, delaying diagnosis and therapeutic decisions, such as implementation of RRT. It is very important, as early stages of renal injury are asymptomatic. Lack of an early marker of renal injury diminishes the likelihood of implementing effective treatments that might at least reduce the extent of damage and improve the prognosis. The most desirable features of such a biomarker include: simplicity, standardization and wide availability of urine and serum measurements, detectability during early hours after the insult, and appropriate sensitivity and specificity.

As in other populations, among patients after OLT, neutrophil gelatinase-associated lipocalin (NGAL) is the most often used biomarker of renal tubule injury.

NGAL

NGAL is a broadly expressed, small protein with molecular weight of 25 kDA. It was first detected in the granules of activated neutrophils and in macrophages, from which it is released in the course of inflammation as an acute-phase protein. Under physiological conditions, trace expressions of NGAL were identified in renal tubular epithelium, as well as in the lungs, liver, and gastrointestinal tract [16]. NGAL is filtered in renal glomeruli and subsequently reabsorbed in proximal tubules. In AKI, urinary NGAL excretion increases shortly after the appearance of an ischemic or toxic factor due to the damage to proximal tubules, as well as a significant increase in expression of NGAL mRNA and protein, both in the loop of Henle and the distal tubule [16,17]. This elevation persists for the next several hours or more. Simultaneously, an increase in serum NGAL concentrations is observed [17]. An increase in NGAL synthesis appears to protect the tubular epithelium, reducing ischemia-reperfusion injury, improving tubular regeneration, and inhibiting epithelial apoptosis through formation of complexes with siderophores and iron [17,18]. It is the most-studied biomarker, easily detected in urine and serum using ELISA. Clinical trials demonstrated the utility of its measurement in urine (uNGAL) and serum (pNGAL) as an early marker of AKI among adult and pediatric patients across various populations: after cardiosurgical procedures [19,20], in intensive therapy patients and emergency room admissions [21,22], in patients in septic shock [23], after contrast administration for X-ray examination [24], and in renal transplant patients [25].

In the majority of studies conducted in patients after OLT, NGAL appeared to be a good predictor of AKI. Niemann et al. [26] performed prospective pNGAL measurements in 59 patients undergoing OLT in 2 centers. Three blood samples were collected: at baseline immediately after induction of anesthesia (pNGAL1), at 2 h (pNGAL2), and at 24 h after reperfusion (pNGAL3). AKI was defined according to RIFLE criteria, and some

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Table 1. AKI classification according to RIFLE, AKIN and KDIGO criteria [14].

	RIFLE SCr criterion		AKIN SCr criterion		KDIGO SCr crtiterion	RIFLE/AKIN/ KDIGO Urine output criterion
Risk	≥1.5-fold increase from baseline SCr or decrease in GFR ≥25%	Stage 1	≥0.3 mg/dL increase or ≥1.5-fold increase from baseline SCr within 48 hrs	Stage 1	≥0.3 mg/dL increase within 48 hrs or 1.5–1.9 times the baseline within 7 days	<0.5 mL/kg/h for >6 hrs
Injury	≥2-fold increase from baseline SCr or decrease in GFR ≥50%	Stage 2	≥2-fold increase from baseline SCr	Stage 2	2.0–2.9 times the baseline within 7 days	<0.5 mL/kg/h for ≥12 hrs
Failure	≥3-fold increase from baseline SCr or increase to ≥4.0 mg/dL or decrease in GFR ≥75%	Stage 3	≥3-fold increase from baseline SCr or increase to ≥4.0 mg/dL with an acute increase of >0.5 mg/dL or initiation of RRT	Stage 3	≥3 times the baseline within 7 days or increase to ≥4.0 mg/dL with an acute increase of >0.5 mg/dL or initiation of RRT	<0.3 mL/kg/h for ≥24 hrs or anuria for ≥12 hrs
Loss	Persistent renal failure >4 weeks		–		–	–
ESRD	Persistent renal failure >3 months		–		–	–

SCr – serum creatinine; GFR – glomerular filtration rate; RRT – renal replacement therapy.

patients presented with renal dysfunction before the surgery. Among patients with baseline serum creatinine <1.5 mg/dL, the risk stage was noted in 50% of patients and the injury stage was noted in 33% of subjects. In this group, pNGAL concentration at 2 h after reperfusion turned out to be an important predictor of AKI, characterized by satisfactory sensitivity and specificity with AUC of 0.79 and the cut-off point set at 139 ng/mL.

Portal et al. compared the prognostic significance of pNGAL and uNGAL for the development of AKI after OLT. In order to assess that, the investigators measured pNGAL in 80 patients and uNGAL in 40 patients [10]. Blood samples were collected during the first day after OLT (day 0) and 48 h later. AKI was defined according to AKIN criteria, and severe AKI was defined as stage 2 and 3. Postoperative AKI occurred in 30 of 80 patients (37.5%). Risk factors for its development included: day 0 serum creatinine, uNGAL, pNGAL, urine cystatin C concentrations (uCys C), APACHE II (*Acute Physiology and Chronic Health Evaluation II*) scores, and SOFA (*Sequential Organ Failure Assessment*) scores. In multivariate regression analysis, 2 of them – APACHE II >13 (OR 1.64/point; 95% CI, 1.22–2.21, P=0.001) and pNGAL (OR 1.01/ng/mL; 95% CI, 1.00–1.02, P=0.002) – were independent predictors of AKI and severe AKI. The best combination of specificity and sensitivity was associated with pNGAL concentrations >212 ng/mL and >258 ng/mL, respectively. Presence of both parameters (APACHE II >13 and pNGAL >258 ng/mL) was associated with the risk of development of severe AKI as high as 79%. If 1 of them was identified, the risk was 40%, while no AKI episode was noted in the remaining patients. Both uCys C and uNGAL had significantly poorer prognostic value, although this could have been because the study group size was only half as large. Limitations of the study included variable times of collection of blood and urine samples, and a single measurement. Nevertheless, pNGAL turned out to be a strong predictor of AKI after OLT.

Wagner et al. measured uNGAL in 92 patients before surgery, immediately after graft reperfusion, and at 3, 18, and 24 h later [27]. AKI was defined as an increase in creatinine concentration by >50% (RIFLE criteria). While uNGAL differentiated between patients with and without AKI after as much as 24 h, uNGAL level corrected for urinary creatinine (uCr) was significantly increased after 3 h and then 18 h following reperfusion. Receiver operating characteristic (ROC) analysis showed the high predictive value of uNGAL/uCr ratio: AUC 0.800 at 3 h and 0.636 at 18 h after reperfusion. The authors determined the best cut-off values for uNGAL/uCr were at 3 h (as 0.74, with sensitivity of 83.5% and specificity of 67.5%) and at 18 h (as 0.35, with sensitivity of 68.1% and specificity of 59.7%). The diagnostic utility of uNGAL/uCr as a biomarker of AKI among patients after OLT was corroborated by Jeong et al. in a smaller group of 19 patients undergoing living-related liver

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transplantation [28]. They compared the predictive value of pNGAL and uNGAL/uCr among patients with AKI diagnosed according to RIFLE criteria: sCr ≥50% increase from baseline. The authors assumed at least a 50% increase in corrected uNGAL and pNGAL levels relative to baseline as a criterion for the diagnosis of AKI based on NGAL. Such a ≥50% increase was observed for pNGAL/uCr only in 8 of 11 patients, while for uNGAL/uCr, it was observed in all of them. The uNGAL/uCr ratio increased at 2 h after reperfusion, reaching peak values at 3 h (P=0.001), and subsequently dropped. There was also an increase in pNGAL values up to 10 h after reperfusion, although it did not reach statistical significance. The authors concluded that in patients after OLT, corrected uNGAL might be a more sensitive marker of AKI than pNGAL, although this requires confirmation in larger studies. Both studies point to the need for correcting uNGAL for uCr levels, to eliminate a possible effect of urine concentration/dilution. During OLT, patients often require massive fluid transfusions, which might increase urine volume and dilution of substances dissolved in it.

Not all studies yielded unequivocally positive results. Kohsravi et al. evaluated pNGAL twice - before surgery (pNGAL1) and 2 h after reperfusion (pNGAL2) – in 90 patients undergoing OLT [29]. AKI defined as an increase in serum creatinine concentration ≥0.3 mg/dL over 48 h, corresponding to stage 1 according to AKIN and KDIGO, was diagnosed in 34% of subjects. Analysis of the results demonstrated that ΔNGAL was predictive for AKI but pNGAL2 concentration was not. While the authors suggested that pNGAL is a useful biomarker for prediction of AKI development after OLT, it should be noted that in the ROC analysis, the AUC for ΔNGAL during the first 48 h was relatively small (0.64). In a study by Iguchi et al., who measured pNGAL, uNGAL/uCr and L-FABP/uCr in 25 different organ transplant recipients (heart – 9, lungs – 6, liver – 10) immediately after admission to the ICU and then every 24 h, none of the above biomarkers turned out to be a predictor of AKI development [30].

Other Biomarkers

In the recent years there have also been studies investigating the utility of other serum and/or urine biomarkers, such as kidney injury molecule 1 (KIM), L-type fatty acid-binding protein (L-FABP), interleukin-18 (IL-18), netrin 1, and semaphorin-3A, in patients after OLT.

KIM-1

KIM-1 is a transmembrane glycoprotein with a molecular weight of 38.7 kD, expressed in the epithelium of proximal tubules in response to ischemia-reperfusion injury, toxic factors, or inflammation. Extracellular domain of KIM-1 is shed due to the action of matrix metalloproteinases [31] and appears in urine shortly after the insult [32]. Since KIM-1 is not found in urine under normal circumstances, its presence always indicates kidney damage. Results of experimental studies were very encouraging [32], but clinical studies were less so. They corroborated the utility of uKIM-1 in early diagnosis of AKI in adults and children undergoing cardiac surgery [33,34], critically ill patients [35], after patients with sepsis [36], drug nephrotoxicity [37], or after renal transplantation [38], although it was characterized by a weaker discriminating power than NGAL.

A large prospective multicenter study – TRIBE-AKI (Translational Research Investigating Biomarker Endpoints in AKI) – assessed the diagnostic significance of 2 biomarkers, uKIM-1 and uL-FAB, in 1219 adults and 311 children after cardiosurgical procedures in 11 academic centers in the USA [39]. AKI was defined as doubling of serum creatinine or need for acute dialysis. Both uKIM-1 and uL-FABP peaked after surgery, but not significantly when adjusted for other biomarkers (uNGAL and uIL-18). The ability to predict AKI was much higher when uKIM-1 was combined with uL-FABP, with an AUC of 0.93, a positive predictive value of 63%, and sensitivity of 77% [40]. The results of systemic analysis of 11 studies with a total of 2979 patients suggest that the efficiency of uKIM-1 for AKI diagnosis depends on the population setting, with the best results after ischemic injury, especially in children, who are not biased by several comorbidities such as diabetes mellitus, hypertension, or concomitant conditions (e.g., sepsis) [41].

Dedeoglu et al. compared the utility of pNGAL, uNGAL, uKIM-1, and glutathione s-transferase (uGST) in early detection of AKI in 26 adults after OLT [42]. The study confirmed the high predictive value of pNGAL (AUC 0.84 at 4 h and 0.86 at 8 h after ICU admission), and the somewhat weaker value of uNGAL (0.79 right after the procedure, 0.80 at 4 h, and 0.76 at 8 h after ICU admission), while uKIM-1 and uGST failed to detect AKI. Similar results were obtained in a recent study by Tudoroiu et al. [43].

L-FABP

L-FABP is a small protein located in the cytoplasm of proximal tubule epithelium. It is involved in transport of fatty acids into the mitochondria, where they serve as a source of energy and protect against oxidative stress. Ischemic or oxidative damage leads to increased tubular and urinary expression of L-FABP. Several studies evaluating patients after cardiac surgery and ICU patients showed the usefulness of uL-FABP (AUC 0.70–0.95) in early diagnosis of AKI defined according to RIFLE or AKIN criteria [44,45].

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Li et al. compared the diagnostic value of uNGAL and uL-FABP, both expressed as a ratio to uCr (ng/mg uCr), in 25 patients after OLT. Concentrations of uNGAL/uCr were significantly higher at 2, 4, and 6 h ($P<0.05$) after reperfusion in patients with AKI, while concentrations of uL-FABP/uCr were elevated only at 6 h after reperfusion [46]. ROC analysis demonstrated AUCs for uNGAL: 0.766, 0.773, and 0.773 after 2, 4, and 6 h, respectively, and only 0.760 after 4 h for uL-FABP. On the other hand, Ichugi et al. failed to show the utility of uL-FABP in predicting AKI among patients after OLT [30]. Thus, it appears that further studies are necessary.

IL-18

IL-18 is a proinflammatory cytokine synthesized by a variety of cells, including monocytes, macrophages, and epithelial cells of proximal tubules, from where they are excreted to urine in response to injury. IL-18 (uIL-18) is found in urine within several hours after cardiovascular procedures among children with AKI [47]. While in some studies, uIL-18 was found to be a good predictor of AKI among patients with acute respiratory failure [48], after renal transplantation [25], or cardiac surgery [47,49], other studies showed moderate or negligible utility [50–52]. The diagnostic accuracy for AKI tends to be more effective in pediatric patients [53].

Sirota et al. examined serum IL-6, IL-8, and urine IL-18, NGAL concentrations in 40 patients before and within 24 h after OLT [54]. AKI, defined as sustained increase in serum creatinine by ≥50% relative to preoperative values within 24 hours, was diagnosed in 7 (17.5%) of them. Significant increases in postoperative uIL-18 (AUC 0.749), uNGAL (AUC 0.833) and uIL-8 (AUC 0.773) as well as pIL-8 (AUC 0.742) were observed in this group. The authors postulated the need for assessing a broad panel of AKI biomarkers after OLT.

In another study, Sung et al. evaluated the significance of pIL-18 as a predictor of AKI after OLT [55]. They found that AKI developed in 12 of 26 patients (46%) (AKIN criteria). Results were promising – the AUCs of pIL-18 were 0.842 at 2 h, 0.905 at 4 h, and 0.726 at 24 h after reperfusion.

Netrin-1 and Semaphorin-3A

Netrin-1 and semaphorin-3A are low-molecular proteins that control cell migration and neuronal regeneration [56,57]. However, they are also significantly expressed in many organs, including the kidneys. It is thought that netrin-1 protects against ischemic and inflammatory damage, while semaphorin-3A most probably plays a pathogenic role [58,59].

Experimental studies demonstrated the presence of netrin-1 in urine as early as 1–3 h after an ischemic or toxic injury [60]. However, these were only single-center clinical studies on the role of this biomarker in the prediction of AKI. Ramesh et al. examined 60 patients after cardiopulmonary bypass (CPB), 26 of whom developed AKI (RIFLE criteria) [61]. They observed a significant increase in uNetrin concentration corrected for uCr in this group. It was highest at 6 h after CPB (2462±370 pg/mg uCr), and AUCs at 2, 6, and 12 h after CPB were 0.74, 0.86, and 0.89, respectively. Tu et al. assessed the utility of uNetrin and uKIM-1 in the early diagnosis of AKI among 150 patients with sepsis [36]. They found a very high predictive value of both of them, with AUCs of 0.858 at 3 h for uNetrin-1 and 0.916 at 24 h for uKIM-1.

Jayakumar et al. examined the significance of semaphorin-3A as a biomarker of AKI in an animal model and then in 60 children who underwent cardiac surgery, 26 of whom (43%) developed AKI (RIFLE criteria) [62]. Urine semaphorin-3A increased at 2 h after CPB and peaked at 6 h (2596±591 pg/mg uCr), with a significant predictive power with AUCs 0.88, and 0.81 at 2 and 6 h after CPB, respectively. Urinary semaphorin-3A turned out to also be a good biomarker for prediction of contrast-induced AKI among adults undergoing percutaneous coronary intervention [63]. The study included 168 subjects; in 20 patients with AKI (RIFLE criteria), semaphorin-3A and NGAL urinary levels corrected for uCr increased significantly at 2 and 6 h after surgery. Based on ROC analysis, the authors established cut-off values at 2 h as follows: 389.5 pg/mg uCr for semaphoring-3A with 94% sensitivity and 75% specificity and 94.4 ng/mg uCr for NGAL with 74% sensitivity and 82% specificity.

The significance of netrin-1, semaphorin-3A, and NGAL for early diagnosis of AKI after OLT was also studied by Lewandowska et al. [64]. AKI (RIFLE criteria) occurred within 3 days after the surgery in 35 (56%) of 63 patients included in the study. Some of them had impaired renal function at baseline. Urinary concentrations of all 3 biomarkers were examined in relation to serum creatinine levels. They increased in patients with AKI, reaching peak values as early as 2 h after the procedure and their predictive power expressed as AUC amounted to 0.66 for netrin-1, 0.63 for semaphorin-3A, and 0.65 for NGAL.

Conclusions

There is an ongoing search for reliable biomarkers enabling early identification of patients at risk of development of AKI and severe AKI in many clinical situations. It has often been compared to the search for troponin 1 in myocardial infarction. However, the situation is much more complicated because, unlike myocardial infarction, AKI is not a single disease, but is rather a multifactorial, heterogeneous clinical

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syndrome associated with a number of pathophysiological processes coexisting in various combinations. Thus, different biomarkers might be useful in AKI due to sepsis, and other after the administration of contrast agents, or in AKI after cardiac surgery. Still, in such cases we are dealing with relatively homogeneous groups of patients and the moment of injury is predictable and easy to monitor. The situations which pose the most difficulty are these when AKI develops in heterogeneous populations (e.g., with various comorbidities), and its pathogenesis is complex, just like in patients after OLT, when its development can be affected by a variety of factors occurring at different times.

Further large prospective studies are clearly needed to simultaneously measure several urine and plasma biomarkers, to identify the one or, more likely, a combination of them, that would have added value for early detection of AKI in this specific population.

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