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Publication Date

2022-08-01

DOI

10.1016/j.plabm.2022.e00278
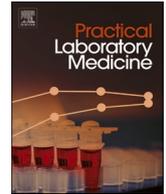
Role of proenkephalin in the diagnosis of severe and subclinical acute kidney injury during the perioperative period of liver transplantation☆

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ABSTRACT

In recent decades, clinical research on early biomarkers of renal injury has been frequent and intensive, with proenkephalin (PENK) being indicated as a promising filtration biomarker (BM). From a cohort of 57 patients, blood samples were collected preoperatively and 48 h after liver transplantation (LT). The following BMs were analyzed: PENK, cystatin-C (CYS-C), and serum creatinine (Scr). Diagnosis of AKI was based on the KDIGO criteria. Of the 57 patients undergoing LT, 50 (88%) developed acute kidney injury (AKI) and were categorized as follows: no-AKI/mild-AKI - 21 (36.8%) and severe-AKI 36 (63.2%). During the preoperative period, only PENK was significantly higher in patients with severe AKI, with an AUC of 0.69 (CI 0.54–0.83), a cutoff of 55.30 pmol/l, a sensitivity of 0.86, a specificity of 0.52, and an accuracy of 0.75. In addition, subclinical AKI was determined preoperatively in 32 patients. Forty-eight hours after LT, PENK maintained its performance in determining severe AKI, with an AUC of 0.83 (CI 0.72–0.94), a cutoff of 119.05 pmol/l, a sensitivity of 0.81, a specificity of 0.90, and an accuracy of 0.84. PENK detected AKI 48 h earlier than serum creatinine. In a multivariate linear regression analysis, PENK was an independent predictor of severe AKI. This small study suggests that the filtration biomarker PENK shows promise for detecting AKI in patients undergoing LT, revealing greater accuracy and an earlier rise in patients with severe AKI. The combination of kidney functional and filtration BMs may aid in the management and prevention of AKI progression.

1. Introduction

Liver transplantation (LT) is the only treatment available for patients with end-stage liver disease, such as liver cancer or acute and subacute liver failure [1]. The United States has the largest volume of transplants, with more than 7000 cases per year, and the second

most active country is China, followed by Brazil [2]. Among the various types of postoperative organ damage, acute kidney injury (AKI) is particularly prevalent, developing in 5–20% of patients undergoing major noncardiac surgery; in LT, the incidence of AKI is high, reaching 50% in some studies [3–6].

The diagnosis of AKI was based on the Kidney Disease Improving Global Outcomes (KDIGO) criteria: changes in serum creatinine and urine output [7]. The problem is that the limitations in cirrhotic patients are more severe due to malnutrition, changes in liver metabolism, dehydration, and decreased muscle mass, which makes the diagnosis of AKI even more difficult and often delayed [8]. In addition, the use of urine output is not recommended by the *International Club of Ascites* (ICA) [9]. The diagnosis of AKI is usually delayed, hindering the effectiveness of medical treatments.

AKI is usually a common complication after LT and is associated with decreased graft viability and the risk of developing chronic kidney disease (CKD) and/or progression to end-stage renal disease (ESRD) and, consequently, lower survival [10–13]. Several promising biomarkers have been identified over the years to try to identify this syndrome earlier. Previous studies have reported the applicability of the biomarker (BM) in the LT setting [14–20]. Nevertheless, few studies have evaluated BMs in glomerular filtration. The most common forms available that estimate the glomerular filtration rate (eGFR) are the *Modification of Diet in Renal Disease* (MDRD) and *Chronic Kidney Disease Epidemiology Collaboration* (CKD-EPI), which are not ideal because the loss of renal function does not correspond to the degree of decline in eGFR and does not reflect tubular function. Exogenous filtration markers are more accurate, and inulin, iothalamate, CrEDTA or iohexol can provide a more reliable estimate of filtration but need to be injected, making the process time-consuming and costly [21].

Proenkephalin A 119–159 (PENK) was recently described to be a reliable BM of renal function, with a long half-life in vivo, stability after collection, and levels that are not influenced by age or sex [22]. In addition, it is not a plasma-bound protein and, therefore, is exclusively filtered in the glomerulus, making it a promising BM for the analysis of renal function in critically ill patients [23].

As AKI is a common occurrence after LT and with the lack of studies of BMs, we hypothesized that PENK and plasma cystatin (CYS)-C in the preoperative period and 48 h after the transplantation period could be a prognostic tool to determine the severity of AKI, the need for renal replacement therapy (RRT) and mortality. To our knowledge, this is the first study to report the performance of filtration BMs in LT with sufficient events requiring RRT and other outcomes, evaluated in clinical practice and thus suggesting the establishment of cutoff values. In addition, few studies appear to have evaluated filtration BMs with the possibility of predicting the need for RRT and mortality.

2. Materials and methods

The University of Sao Paulo Ethics Committee approved the study under protocol number CAAE:06636513.4.0000.0068. All clinical and research activities being reported are consistent with the Principles of the Declaration of Istanbul and with the Declaration of Helsinki. The protocol is registered in Clinical Trials being available at https://clinicaltrials.gov by the identifier NCT 02095431.

2.1. Patients

During a 24-month period, from June 2013 through June 2015, all planned liver transplant recipients (LT) at University of Sao Paulo, Brazil, were screened prior to surgery for enrollment. The exclusion criteria were as follows: age less than 18 years, need for dialysis preoperatively, combined liver and kidney transplant, chronic kidney disease stage 5, and previous kidney or liver transplant. One hundred eligible patients were enrolled after voluntary informed consent was obtained as per the guidelines of the Institution Ethics Committee.

Of this cohort, we selected 57 patients undergoing LT to include in our analysis. We selected the most severe patients for analysis with KDIGO 3 and the need for RRT versus KDIGO 0 and 1.

We recorded the baseline kidney function and comorbid history from the electronic medical records (EMRs). The following perioperative variables included main patient characteristics, intraoperative data, clinical follow-up in the first week after LT, need for RRT data and outcomes.

The functional MELD was calculated based on the serum bilirubin, international normalized ratio (INR) and serum creatinine according to the formula score MELD = 0,957 × Loge (creatinine mg/dl) + 0,378 × Loge (bilirubin mg/dl) + 1120 × Loge (INR) + 0,643 × 10. The LT MELD is the result of the sum of the value of functional MELD with scores in special situations of transplant priority (15).

Blood and urine samples were collected simultaneously in the perioperative period of LT, before induction of anesthesia, intra-operatively (after portal reperfusion), and 6, 18, 24 and 48 h after surgery. We recorded vital signs, the process of care and lab results daily for 7 days after LT. Outcomes, including maximum AKI severity stage (KDIGO 1,2,3), need for RRT in the first week and mortality 60 days after liver transplant, were assessed in the intensive care unit (ICU) until hospital discharge. All measured biomarkers were blinded to the investigators.

2.2. Clinical outcomes

The primary outcome was AKI development during the first week of LT. Baseline renal function was defined as the lowest value in the last three months and was used to assess renal recovery. AKI diagnosis was based on the Kidney Disease Improving Global Outcomes (KDIGO). We considered reference serum creatinine as the lowest value during the week before liver transplantation, and this value was used to determine the AKI diagnosis. AKI stage was defined according to KDIGO: stage 1 (1.5–1.9 times the sCr reference, or

an increase =>0.3 mg/dl up to 48 h), stage 2 (2.0–2.9 times the sCr reference), and stage 3 (3.0 times the sCr reference or an increase >4.0 mg/dl). Patients with no AKI or stage 1 AKI were categorized as having no/mild AKI, whereas patients meeting the criteria for stage 2 or 3 AKI seven days after LT were identified as having severe AKI.

2.3. Biomarker collection and measurement

Blood samples were collected from central venous catheters or arterial lines, and urine was collected through indwelling catheters. After collection, samples were immediately centrifuged: blood samples were subjected to 3000 rotations per minute (r.p.m.) for 15 min and stored at −80 °C until analysis.

The Sphingotest® penKid® immunoassay kit (PEK96) measures plasma Proenkephalin119-159, a stable surrogate for the kidney stimulating hormone enkephalin, by immunoluminometric assay in pmol/l.

The biomarker cystatin C was measured in urine (diluted 5-fold) and plasma (diluted 50-fold) using a BioLegend (445507) kit (San Diego, CA, USA).

Serum creatinine was measured by the automatic kinetic method. A Roche kit n° 06407137190 and the Roche Cobas c720 analyzer were used.

All measured biomarkers were blinded to the investigators.

2.4. Statistical analysis

Continuous variables are presented as the mean ± standard deviation (SD) or median (25th–75th percentiles) and were compared using one-way ANOVA or the Kruskal–Wallis test according to the Gaussian distribution. Categorical variables are presented as absolute numbers and percentages and were compared by the chi-square test. P values were two tailed, and $P < 0.05$ was considered significant. Conventional receiver operating characteristic (ROC) curves were generated, and the area under the curve (AUC) was used to assess the ability of continuous variables to distinguish the categorical state: AKI development, need for dialysis and nonsurvival. The optimal cutoffs were determined by the best point of sensitivity versus the specificity of the AUC (Youden index).

We compared the time to AKI diagnosis based on biomarkers versus creatinine analyzed by chemiluminescence in the same sample collection. Time to diagnosis based on the sCr criterion was assessed by the KDIGO stage 1 definition, and biomarkers were determined by the cutoff value PENK. Perioperative covariates were tested in the univariate analysis for their impact on AKI development, need for RRT and nonsurvival. Factors associated with the outcomes at $P < 0.01$ were used to construct a multivariable model, in which the impact of each comorbidity or covariate was adjusted. SPSS (Statistical Package for Social Sciences) version 20 (Chicago, Illinois) software was used for the statistical analysis.

3. Results

3.1. Patient characteristics

Fifty-seven patients undergoing LT were included in our analysis. We selected the most severe patients for analysis with KDIGO stage 3 (KDIGO 3) and the need for RRT versus KDIGO stage 0 and 1. Based on the baseline outpatient Scr values, 23 patients (67.6%) were in KDIGO stage 1 before surgery; however, no patient in the cohort had a Scr greater than 1.5 mg/dl preoperatively or a higher disease stage with a KDIGO stage of 2 or 3.

The demographic and clinical characteristics of the patients are shown in Table 1. Patients who did not develop AKI or achieved KDIGO stage 1 AKI during the first 7 days of LT were categorized as having no AKI/mild AKI, comprising 21 (36.8%) patients, while patients who had KDIGO stage 2 or 3 AKI during the first 7 days of LT were categorized as having severe AKI 36 (63.2%).

Table 1
Demographic characteristics and outcomes.

	Total	No AKI/Mild AKI	Severe AKI	P
AKI	57 (100)	21 (36,3)	36 (63,2)	
Age	58 (12,25)	56,80 (12,81)	54 (11,13)	0,123
Gender	35 (61,4)	16 (45,71)	19 (54,29)	0,09
BMI	26 (4,38)	25,67 (3,14)	26,05 (5,18)	0,476
time anesthesia	09:05 (01:56)	09:05 (01:16)	10:27 (02:10)	0,009
Urine output	488 (432)	667 (469)	376 (369)	0,001
Fluid balance	1555 (1212)	1156(95O)	1643 (1326)	0,1
SOFA	13 (11–15)	12 (9–12)	14 (12–16)	<0,001
MELD	29 (29–29)	27,67 (3,37)	29,25 (3,33)	0,044
Need for RRT	21 (36,8)	01 (4,8)	20 (95,2)	<0,001
Mortality	10 (17,5)	0 (0)	10 (100)	0,008

Data are expressed as n (%), mean SD (±), median and percentile (25–75) according to their distribution. The time of the anesthesia were representing hours: minutes. BMI (body mass index), SOFA (Sequential Organ Failure Assessment), MELD (model for end-stage liver disease), RRT (renal replacement therapy).

Table 2
Progression of PENK, CYS and Scr in severe AKI, need for RRT and mortality groups.

	N	No-AKI/Mild AKI	Severe - AKI	p	Without RRT	Need for RRT	P	Survivors	Nonsurvivors	P
Pré - P CYS (mg/l)	51	0,76 (0,61–1,44)	1,05 (0,68–1,55)	0,251	0,80 (0,61–1,39)	1,11 (0,48–1,53)	0,89	0,83 (0,61–1,42)	1,01 (0,69–1,31)	0,48
Pós - P CYS (mg/l)	51	0,45 (0,43–0,56)	1,55 (0,49–2,38)	0,09	0,46 (0,43–1,03)	0,83 (0,45–2,00)	0,33	0,51 (0,45–1,03)	1,10 (0,68–1,57)	0,74
Pré PENK (pmol/L)	57	55,00 (42,25–94,55)	90,16 (64,70–135,78)	0,03	67,27 (51,75–106)	100 (65–162,34)	0,10	81 (54–115,80)	83,90 (63,66–271)	0,11
Pós PENK (pmol/L)	57	81,00 (61,25–101,50)	161,45 (122,85–294,03)	0,01	93,75 (62–159)	194,44 (143–311)	0,01	120,10 (73–205)	159,50 (100–337)	0,31
Pré SCR (mg/dl)	55	0,82 (0,73–1,00)	1,00 (0,77–1,45)	0,136	0,93 (0,75–1,07)	1,00 (0,73–1,57)	0,265	1,00 (0,77–1,09)	1,11 (0,65–1,52)	0,39
Pós SCR (mg/dl)	57	1,00 (0,74–1,92)	1,82 (1,00–2,40)	0,087	1,36 (1,00–2,06)	1,96 (1,00–2,44)	0,209	0,45 (0,33–0,91)	0,55 (0,43–1,78)	0,678

3.1.1. Performance of PENK, Scr and CYS-C for the diagnosis of AKI in the perioperative period of LT

In the preoperative period, patients with severe AKI had PENK levels 1.6 times higher than those in the no-AKI/mild-AKI group, and the only BM that reached statistical significance in the preoperative period was the PENK P = 0.03, with a median of 55.00 (P25/75: 42.25–94.55) in the no-AKI/mild-AKI group versus 90.16 (P25/75: 64.70–135.78) in the severe-AKI pmol/l group (Table 2), with an AUC of 0.69 (95% CI 0.54–0.83), a cutoff value of 55.30 pg/ml to predict severe AKI, a sensitivity of 86%, a specificity of 52% and an accuracy of 75%. Forty-eight hours after LT, the difference in medians between the groups was more evident, with a PENK level of 81.00 (P25/75: 61.25–10.50) in the no-AKI/mild-AKI group vs. 161.45 (P25/75: 122.85–294.03) pmol/l in the severe-AKI group (Fig. 1, Table 2). The best performance of PENK was 48 h after LT, with an AUC of 0.83 (95% 0.72–0.94) (P = 0.001), a cutoff value of
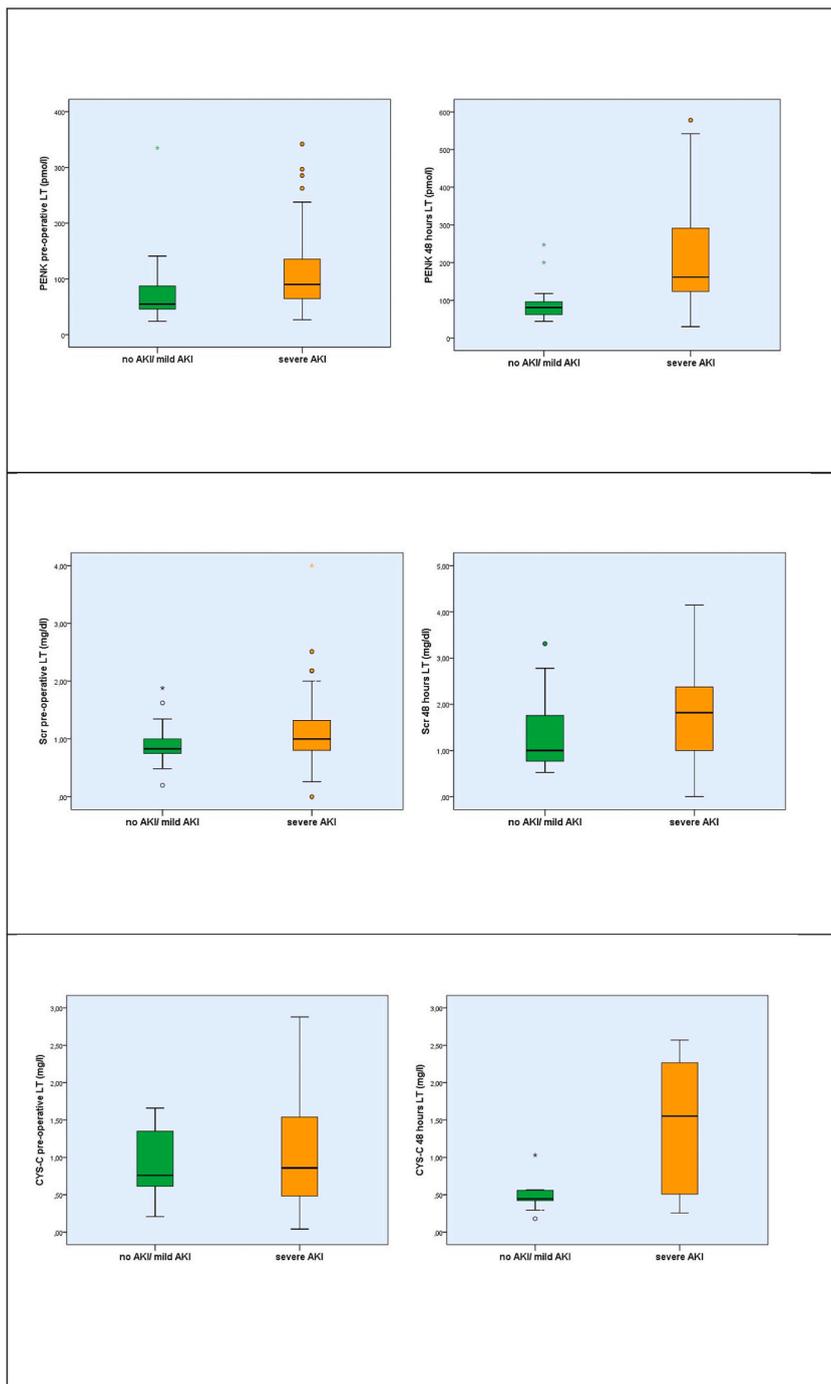

Fig. 1. Levels of PENK, Scr and CYS-C pre- and 48 h after LT in the AKI groups.

119 pmol/l to predict severe AKI, a sensitivity of 81%, a specificity of 90% and an accuracy of 84%.

Preoperatively, the median value of Scr was higher in the group with severe AKI than in the group no-AKI/mild AKI, but the difference was not significant. Forty-eight hours after LT, the Scr levels were approximately 2 times higher in patients with severe AKI (median, 1.00 mg/dl in no-AKI/mild-AKI vs. 1.82 mg/dl in severe-AKI, P = 0.087), with an AUC of 0.67 (95% CI 0.51–0.82) (Table 2). The CYS-C levels were higher in severe AKI but without statistical significance (Table 2).

3.1.2. Subclinical severe AKI

We evaluated positivity and the time to AKI diagnosis based on PENK cutoff values and sCr KDIGO criteria in the preoperative period. For this analysis, we used sCr measured by chemiluminescence in the same samples as the biomarkers. AKI diagnosis was reached by sCr in twenty-two patients and by PENK levels (with a cutoff of 55 pmol/l) in forty-one patients. The group end is available in Fig. 2, and the outcomes according to groups are shown in Fig. 3. The most interesting group was the subclinical AKI, where diagnosis was only possible by BM PENK and not by Scr, which occurred in 32 patients. It was also the group that better indicated the need for RRT and mortality. Additionally, the median time based on PENK diagnosis was 48 h earlier than that based on Scr.

3.1.3. PENK, Scr and CYS-C performance in requiring RRT in the perioperative period of LT

Twenty-three patients required RRT during hospitalization, and 21 patients (36.8%) required RRT in the first week after LT. The best performance of PENK in predicting the need for RRT was in the postoperative period at 48 h, with a median of 93.75 (P25/75: 62–159) in the group without RRT versus 194.44 (P25/75: 143–311) in the group requiring RRT pmol/l, with an AUC of 0.76 (95% CI 0.63–0.89), a cutoff point of 131 pmol/l, a sensitivity of 81% and a specificity of 72% (Table 2, Fig. 4). The median Scr and CYS-C were higher in the group requiring RRT than in the group without RRT, but the differences were not significant (Table 2).

3.1.4. Performance of PENK, Scr and CYS-C to determine mortality in the perioperative period of LT

The 60-day mortality was 10 (17.5%), with no deaths in the no-AKI/mild-AKI group and 10 (100%) deaths in the severe-AKI group (P = 0.009). During the preoperative period, the median level of PENK was similar between survivors and nonsurvivors (81 vs. 83.9 pmol/l). Forty-eight hours after LT, the expression level of PENK was higher in nonsurvivors (159.50 (P25/75: 100–337) vs. 120.10 (P2/75: 73–05) pmol/l) than in survivors, but the difference was not significant. The median Scr and CYS-C were higher in nonsurvivors than in survivors but did not reach significant differences.

3.1.5. Performance of PENK, Scr and CYS-C to predict outcomes in the perioperative period of LT

The logistic regression model was constructed, including age, duration of anesthesia, urine output, fluid balance, model for end-stage liver disease (MELD) on admission to the intensive care unit (ICU) and level of PENK, Scr or CYS-C for each outcome (severe AKI, need for dialysis and mortality).

During the preoperative period, no variable was found to be a predictor of severe AKI. During the postoperative period, only PENK was an independent predictor of severe AKI (PENK: odds ratio (OR) 1.02 (CI 1.00–1.04), P = 0.01; Scr: OR 2.60 (CI 0.98–6.93), P = 0.06). During the preoperative period, independent predictors of RRT need were duration of anesthesia, urine output, fluid balance and PENK (duration of anesthesia, 1.00 (CI 1.00–1.00), P = 0.05; urine output, OR 0.99 (CI 0.99–0.99), P = 0.02; water balance, OR 1.00 (CI 1.00–1.00), P = 0.03; preoperative PENK, OR 1.02 (CI 1.00–1.04), P = 0.019). Scr did not reach statistical significance (OR 3.15 (CI 0.34–28.87), P = 0.31). During the postoperative period, the variables that were independent predictors of the need for RRT were urine output (OR 0.99 (CI 0.99–0.99), P = 0.03), water balance (OR 1.00 (CI 1.00–1.00), P = 0.03), Scr (OR 4.34 (CI 1.07–17.58), P = 0.04), and PENK (OR 1.02 (CI 1.00–1.04), P = 0.06).

In the evaluation of mortality outcome, no variable was found during the preoperative period, but the duration of anesthesia was an independent predictor of mortality during the postoperative period (OR 1.00 (CI 1.00–1.04), P = 0.03).

Fig. 2. Division of Scr and PENK groups by cutoff.

BM+Scr+	5 (23,8%)	3 (30%)
BM+Scr-	12 (57,1%)	5 (50%)
BM-Scr+	1 (4,8%)	0 (0%)
BM-Scr-	3 (14,3%)	2 (20%)

Fig. 3. Groups according to outcomes, columns: first: group; second: need for RRT; third: mortality.
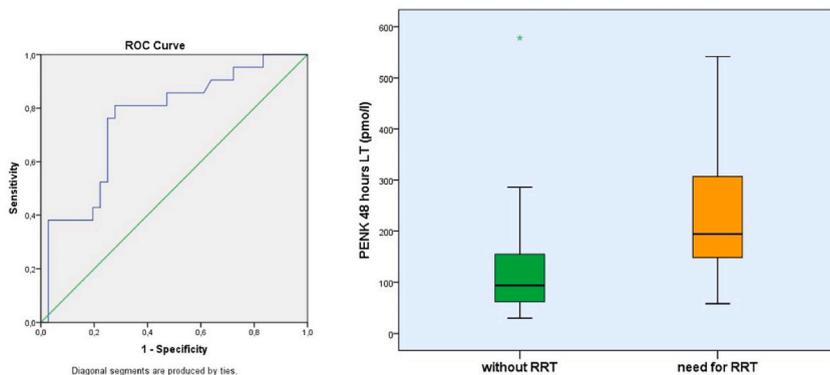

Fig. 4. ROC curve AUC and levels of PENK 48 h after LT in the need-RRT groups.

4. Discussion

The diagnosis of subclinical AKI has always been a challenge, which impacts the planning and advances of treatments in its management, since the subclinical diagnosis can precede renal damage, where the lesion is still progressing. In our study, a kidney injury biomarker (PENK) with a functional biomarker (Scr), together with CYS-C, were used to form a panel of renal filtration BMs. PENK preceded the diagnosis of AKI by Scr over 48 h, revealing the presence of kidney injury during the preoperative period. It was also useful during the postoperative period, as well as for other outcomes, such as the need for RRT, revealing a BM that is more sensitive and specific than CYS-C or Scr.

PENK is a more recent biomarker of glomerular filtration injury, which, unlike CYS-C, is not influenced by inflammation [24,25]. Our results revealed the ability to determine severe AKI even during early periods, such as during the preoperative stage (median, 55.00 (P25/75: 42.25–94.55) in the non-AKI/mild AKI group versus 90.16 (P25/75: 64.70–135.78) pmol/l in the severe AKI group, P = 0.03), while maintaining this ability during the postoperative period (median, 81 (P25/75: 61.25–101.50) pmol/l in the non-AKI/mild AKI group versus 161.45 (P25/75: 122.85–294.03) in the severe AKI group, P = 0.001).

The problem of precocity, although desired, is poorly applied in clinical studies, perhaps due to the difficulty of segmenting serial samples, in addition to the need for intervention with potential renal injury with pre and post collections. In a study evaluating one hundred eleven hospitalized patients with CKD undergoing radiographic contrast procedures, the authors did not find differences in PENK or baseline Scr during the period before contrast, but the PENK delta increased in patients with AKI after use of the PENK contrast on Day 1 (198 pmol/l vs. 121 pmol/l, P < 0.01) [26]. However, the study by Shan et al. [27], including 92 patients undergoing cardiac surgery, corroborates our findings, and preoperative PENK was an independent predictor of AKI (OR 23.8 (95% CI 2–270), P = 0.011). In addition to revealing the need for further studies, including large cohorts, these results lead us to reflect on the following questions:

Would early diagnosis be truly possible before injury or did the patient already have ongoing kidney injury during the preoperative period? Our study compared the standard marker of glomerular filtration Scr with PENK and CYS-C and revealed that PENK detected AKI 48 h earlier than serum creatinine. In the study reported in the previous paragraph in patients with CKD using contrast, the precocity was 24 h with PENK [26]. Studies [28,29] comparing the PENK value with Scr yielded a correlation r = 0.74 or greater. Our correlation was r = 0.46 during the preoperative period and increased to r = 0.50 during the postoperative period. Recalling that the comparison of the BM with Scr should occur as a parameter for the diagnosis of AKI, we should not aim to substitute but rather complement the existing standard marker according to the recommendations of the *Acute Dialysis Quality Initiative* (ADQI), simultaneously combining functional markers with those of damage to the kidneys, expanding the diagnostic criteria for AKI. The results of this study demonstrate that PENK is able to diagnose subclinical AKI, with 32 patients' positivity by BM and negative by Scr, where there is glomerular/tubular damage without functional loss [30].

Few previous studies have used PENK in the setting of AKI, and none in patients with cirrhosis or LT, with most studies focusing on the sepsis setting. In 2015, de Marino et al. [31], with 101 septic patients, found that PENK was independently associated with the diagnosis of AKI. According to the staging with RIFLE, there was an increase in its expression (P = 0.001). In the 2017 study by Kim et al. [32] comprising a larger cohort of 167 patients, the PENK level increased according to the severity of sepsis. A cutoff value was found for the diagnosis of AKI of 154.5 pmol/l, with an AUC of 0.73 (CI 0.65–0.79). In our study, the cutoff value 48 h after surgery was 119.05 pmol/l, and the AUC was 0.83 (95% 0.72–0.94), with a sensitivity of 0.80 and specificity of 0.90.

In 2018, still in the sepsis scenario [33], PENK was a good determinant of AKI. The study also analyzed outcomes, such as the need for RRT and mortality. ORs of 4.0 (CI 3.0–5.4) were found for the need for RRT in the ICU and 1.5 (CI 1.2–1.8) for 90-day mortality. Our study also showed that PENK could determine outcomes, such as the need for RRT, with a median postoperative PENK of 93.75 (CI 62–159) in the group without RRT and 194.44 (CI 143–311) (P = 0.001; OR 1.02 (CI 1.00–1.04), P = 0.06) in the group requiring RRT, but it was not possible to determine mortality at 60 days.

CYS-C is a BM with better accuracy than Scr, as it is not influenced by sex, race or muscle mass, nor is it affected by bilirubin, which is common in cirrhotic patients [34]. In this study, CYS-C was not able to determine severe AKI, need for RRT or mortality. Previous studies [35–38] that included cirrhotic patients also did not achieve good results with the use of CYS-C, a finding that can be partially explained by the use of immunosuppressants, such as glucocorticoids, which alter the production of CYS-C. Additionally, the state of inflammation may also contribute [39–41]. In the study by Sirota et al. [17], in the LT scenario, plasma CYS-C also failed to determine AKI.

This study has several strengths. The prospective analysis allowed the data to be collected consistently, and the diagnosis of AKI was performed within 7 days, while in most studies, the evaluation was restricted to 48 h. The analysis over a period of one week allows a more realistic view of the diagnosis of AKI and reduces the probability of a diagnosis of subclinical AKI. The paired analysis of renal filtration markers such as CYS-C, as well as the standard Scr marker, allows a more holistic view of the potential and drawbacks of each marker. This study also has some limitations: the low number of patients included of only 57, and the severity of this cohort with MELD 29, leading to a higher incidence rate of AKI (88%). Thus, similar to other analyses [42,43], we had a group with severe AKI; therefore, the ability of these BMs in the early stages of AKI was not evaluated. Larger cohorts, including less severely ill patients, other settings, and populations with different incidences of AKI, should be evaluated to confirm our findings.

5. Conclusion

The filtration biomarker PENK was shown to be promising, with greater accuracy and more precocity for severe AKI, including the preoperative period. Although Scr is a later marker, simultaneously combining functional markers with those of damage to the kidneys (Scr) may help in the management and prevention of AKI progression.

Contributions

Authors CL and EM provided the conceptualization of ideas and the evolution of overarching research goals and aims. Authors CL and EM were responsible for data curation, management activities, maintaining research data, formal analysis, application of statistics, acquisition of financial support for the project leading to this publication, design of methodology, administrative management and coordinating the planning and execution of the research activity. All authors CL, DLG, CRF and EM, conducted a research and investigation process; collection of data/evidence and resources; provision of study materials, reagents, patients, laboratory samples and other analytical tools and prepared, created and wrote the original draft and gave final approval of the version to be published. Author EM supervised and had leadership responsibility for the planning and execution of the research activity, including mentorship external to the core team.

Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

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