Review – Renal Disease

The Predictive Role of Biomarkers for the Detection of Acute Kidney Injury After Partial or Radical Nephrectomy: A Systematic Review of the Literature

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Article info

Abstract

Context: Postoperative acute kidney injury (AKI) is a serious complication after kidney surgery, associated with prolonged hospital stay, high morbidity, and mortality. Biomarkers represent a tool of increasing importance to identify renal impairment after partial nephrectomy (PN) or radical nephrectomy (RN) in order to optimize and anticipate the diagnosis of AKI.

Objective: The goal of this systematic review is to investigate current insights on the role of biomarkers in predicting renal impairment in patients undergoing PN or RN.

Evidence acquisition: A systematic review was conducted up to November 30, 2017 through PubMed, Scopus, and Embase databases, to identify eligible studies evaluating the role of biomarkers for the prediction of AKI after PN or RN. The Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) criteria were applied to select articles.

Evidence synthesis: According to the study selection criteria, 10 publications were included with a total number of 728 patients. Incidence of AKI was 26.7% (range: 9–58%). Based on the evidence reviewed, serum cystatin C and urinary neutrophil gelatinase-associated lipocalin (NGAL) showed a significant correlation with serum creatinine rise postoperatively, emerging as potential noninvasive and early biomarkers of AKI in patients undergoing renal surgery. In this setting, serum cystatin C and urinary NGAL have preceded the rise in serum creatinine peak from 3 up to 24 h, even in case of mild renal damage.

Conclusions: The literature underlines the potential usefulness of biomarkers such as cystatin C and NGAL as promising and early tools to predict AKI after PN or RN. However, no strong evidence in support of their use is available to date and further investigations are awaited.

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Patient summary: We looked at the role of biomarkers in predicting renal injury in patients undergoing partial or radical nephrectomy. Serum cystatin C and urinary neutrophil gelatinase-associated lipocalin have emerged as promising noninvasive, accurate, and early biomarkers.

1.   Introduction

Postoperative acute kidney injury (AKI) is an important surgical complication after kidney surgery, with a variable incidence ranging from 5.5% to 34% [1–4].

AKI following partial nephrectomy (PN) and radical nephrectomy (RN) is associated with increased morbidity and mortality, new-onset chronic kidney disease (CKD), worsening of pre-existing CKD, and prolonged hospitalization [1,2]. Despite these burdens of potential severe harms, so far the awareness of the urological community to the onset of AKI after renal surgery is often overlooked and seen only as a transitory functional failure. Renal injury is indeed often subclinical, escaping the detection of available diagnostic tools or being diagnosed with delay, and therefore more accurate tools to anticipate the diagnosis of AKI are strongly needed. A diagnostic strategy for the early management of AKI could favor prompt treatment and its complete regression to avoid sequelae; moreover, the knowledge of the triggers of subclinical and early renal injury should allow for the correction of any reversible factors and intensify the monitoring of patients at risk. This might be particularly important with the affirmation of novel medical therapies for AKI in the next future [5].

At present, renal impairment is diagnosed by merely measuring serum creatinine notwithstanding its poor accuracy. The increase in serum creatinine is indeed a late, poorly sensitive, and specific sign of AKI because it occurs up to 48–72 h after injury, misses subclinical damage remaining stable until >50% of decrease in functioning nephrons, and does not differentiate between prerenal, parenchymal, and obstructive nephropathy [6].

The ability to assess AKI by a noninvasive tool and in its early phase, with accurate graduations of severity and the possibility to differentiate etiology, may improve the understanding of functional outcome after renal surgery with a promising effect on their management.

Several novel biomarkers such as neutrophil gelatinase-associated lipocalin (NGAL), cystatin C, and Kidney Injury Molecule-1 (KIM-1) have shown to potentially enhance accuracy in detecting severity and etiology of AKI, but to date they have been used only for research purposes [6].

The objective of this systematic review is to investigate current insights of the role of biomarkers in predicting renal impairment in patients undergoing surgery for renal tumor.

2.   Evidence acquisition

2.1.   Search strategy

A systematic review has been performed up to November 30, 2017, using PubMed, Scopus, and Embase, to identify eligible studies evaluating the predictive role of biomarkers for AKI after PN and RN, among English-written papers on adult humans.

Abstract and full-text screening and extraction of data were performed by two reviewers independently (G.R. and M.A.). Possible conflicts were resolved by discussion or with an independent arbiter (A.C.).

The Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) criteria were adopted by two investigators (G.R. and M.A.), and discordances were resolved by a third investigator (A.C.). The following search strategy was adopted: ("acute kidney injury" OR "renal impairment" OR "renal function" OR "biomarker" OR "cystatin C", "neutrophil gelatinase-associated lipocalin" OR "Kidney Injury Molecule-1") AND ("partial nephrectomy" OR "radical nephrectomy" OR "nephrectomy" OR "nephron sparing surgery" OR "urology" OR "urogenital"). Randomized clinical trials and retrospective, observational, and comparative studies on humans were included, whereas single case reports and histological studies were excluded. According to the predefined inclusion and exclusion criteria, title and abstracts were screened and articles were categorized.

After reading the abstract, a more thorough assessment was performed by looking at the full texts of the paper. References from the included studies were manually retrieved to identify additional studies of interest.

A new Excel table was built including data from the selected articles and including number of participants, interventions, comparators, outcomes, and study design (PICOS), as indicated by the Systematic Review Guidance of the Centre for Reviews and Dissemination of the University of York (UK) (Centre for Reviews and Dissemination. Guidance for undertaking reviews in health care. www.york.ac.uk/crd/guidance).

2.2.   Outcome measures

Many urinary and serum biomarkers have been proposed for the prediction of AKI following PN or RN: NGAL, KIM-1, cystatin C, albuminuria, and lactase dehydrogenase (LDH). Table 1 summarizes the characteristics of the novel biomarkers and their performance to reveal AKI after PN or RN. Fig. 1 shows urinary and serum biomarkers of AKI in relation to the nephron physiology.

Many urinary and serum biomarkers have been proposed for the prediction of AKI following PN or RN, including NGAL, KIM-1, cystatin C, albuminuria, and LDH among others. The primary outcome was the predictive ability of these biomarkers with respect to the onset of renal injury and AKI, intended as the relationship between the

Table 1 – Characteristics of novel biomarkers of AKI after partial or radical nephrectomy obtained from included studies.

Author (year)	Biomarker (sources tested)	Surgical setting	No. of patients	Age (mean or median [SD] or range)	Comorbidities (CKD, DM)	Median ischemia duration (min)	AKI criteria	AKI incidence	Postoperative biomarker				
									Timing	Significantly associated with AKI	Correlated with	Not correlated with	Proposed timing and cutoff
Schmid (2014) [18]	Cystatin C, serum	PN, RN	31	60 (52–70)	0%, NA	NA	NA	58%	24 h	Yes	GFR at 1 yr	NA	24 h
Shalabi (2017) [19]	NGAL, urine	RN (laparoscopic, open)	30	60–70	NA, 50	NA	SCr >50% increase or by 0.3 mg% from baseline	41% lapar, 12% open	8 h, 24 h	Yes	NA	Pneumoperitoneum	24 h, >150 ng/mg creatinine
	KIM-1, urine	RN (laparoscopic, open)	30	60–70	NA, 50	NA	SCr >50% increase or by 0.3 mg% from baseline	41% lapar, 12% open	8 h, 24 h	No	NA	Pneumoperitoneum	8 h
Chen (2015) [13]	Cystatin C, serum	PN	89	49 ± 12	0%, 9	26	AKIN	31.5%	24 h, 48 h	Yes	NA	NA	24 h
	Beta2-micro, serum	PN	89	49 ± 12	0%, 9	26	AKIN	31.5%	24 h, 48 h	No	NA	NA	24 h
	Alpha1-micro, urine; beta2-micro, urine	PN	89	49 ± 12	0%, 9	26	AKIN	31.5%	24 h, 48 h	No	NA	NA	24 h
	Microalbuminuria, urine	PN	89	49 ± 12	0%, 9	26	AKIN	31.5%	24 h, 48 h	No	NA	NA	48 h
Parekh (2013) [17]	Cystatin C, serum	PN (open)	38	55 (28–84)	10%, NA	32	SCr >50% increase, in 24 h	13%	2 h, 24 h, 48 h	No	NA	Ischemia duration, ischemia type	24 h
	NGAL, serum	PN (open)	38	55 (28–84)	10%, NA	32	SCr >50% increase, in 24 h	13%	2 h, 24 h, 48 h	No	Ischemia duration	Ischemia type	24 h
	NGAL, urine; KIM-1, urine; NAG, urine	PN (open)	38	55 (28–84)	10%, NA	32	SCr >50% increase, in 24 h	13%	2 h, 6 h, 24 h	No	NA	Ischemia duration, ischemia type	24 h
	L-FABP, serum	PN (open)	38	55 (28–84)	10%, NA	32	SCr >50% increase, in 24 h	13%	2 h, 24 h, 48 h	No	NA	Ischemia duration, ischemia type	2 h
	IL-18, urine; microalbuminuria, urine	PN (open)	38	55 (28–84)	10%, NA	32	SCr >50% increase, in 24 h	13%	2 h, 6h, 24 h	No	NA	Ischemia duration, ischemia type	2 h
Koo (2015) [14]	NGAL, urine	PN (laparoscopic, open)	146	53 ± 12	6.8%, 13	21	AKIN	20% lapar, 26% open	3 h, 24 h, 48 h	No	Preoperative normalized uNGAL	Comorbidities, surgery type, ischemia type, ischemia time, eGFR at 6 mo	3 h
Lahoud (2015) [15]	NGAL, urine	PN (open)	49	61 (29–85)	NA, 18	24	SCr >50% increase or by 0.3 mg% from baseline	37%	1 h, 3 h, 8 h, 24 h, 48 h, 72 h	Yes	Longer clamp time, higher RENAL score, more frequent central location of the tumor	NA	8 h, >150 ng/mg creatinine
	KIM-1, urine	PN (open)	49	61 (29–85)	NA, 18	24	SCr >50% increase or by 0.3 mg% from baseline	37%	1 h, 3 h, 8 h, 24 h, 48 h, 72 h	Yes	NA	NA	8 h, >3.5 ng/mg creatinine
	NGAL, serum; KIM-1, serum	PN (open)	49	61 (29–85)	NA, 18	24	SCr >50% increase or by 0.3 mg% from baseline	37%	24 h	No	NA	NA	24 h
Mihaly (2012) [16]	NGAL, serum	PN, RN (robot-assisted laparoscopic)	3	NA	NA	NA	SCr >0.3 mg% increase from baseline, in 48 h	NA	6 h, 12 h	No	NA	NA	6 h
	NGAL, urine	PN, RN (robot-assisted laparoscopic)	3	NA	NA	NA	SCr >0.3 mg% increase from baseline, in 48 h	NA	6 h, 12 h	No	NA	NA	6 h

Table 1 (*Continued*)

Author (year)	Biomarker (sources tested)	Surgical setting	No. of patients	Age (mean or median [SD] or range)	Comorbidities (CKD, DM)	Median ischemia duration (min)	AKI criteria	AKI incidence	Postoperative biomarker				
									Timing	Significantly associated with AKI	Correlated with	Not correlated with	Proposed timing and cutoff
Abassi (2013) [12]	NGAL, urine	PN (open)	27	NR	NA	(Range 6–47)	SCr >50% increase or by 0.3 mg% from baseline	37%	1 h, 3 h, 8 h, 24 h, 48 h, 72 h	Yes	Ischemia duration, higher RENAL score	NA	8 h
	KIM-1, urine	PN (open)	27	NR	NA	(Range 6–47)	SCr >50% increase or by 0.3 mg% from baseline	37%	1 h, 3 h, 8 h, 24 h, 48 h, 72 h	No	NA	NA	8 h
Sprenkle (2013) [20]	NGAL, urine	PN, RN	120	60 (52–70)	20, 14	24	AKIN	17% PN, 47% RN	0 h, 4 h, 8 h, 24–48 h	No	RN	Ischemia duration, ischemia type	12–24 h, >150 ng/ml
Takagi (2012) [21]	LDH, serum	PN (open)	195	58 (19–84)	26, 13	49	RIFLE, decrease in eGFR of 25% from baseline	9%	5 d	Yes	Decrease of eGFR at 3 and 6 mo	Preoperative CKD, clamping time, PPRP, radius component, endophytic/ exophytic, nearness component, location component, CRP, BT	5 d
	CRP, serum	PN (open)	195	58 (19–84)	26, 13	49	RIFLE, decrease in eGFR of 25% from baseline	9%	5 d	No	NA	NA	5 d

AKI = acute kidney injury; BT = body temperature; CKD = chronic kidney disease (eGFR <60 ml/min); CRP = C-reactive protein; DM = diabetes mellitus; eGFR = estimated glomerular filtration rate; GFR = glomerular filtration rate; IL = interleukin; lapar = laparoscopy; KIM-1 = Kidney Injury Molecule-1; LDH = lactase dehydrogenase; L-FABP = liver-type fatty acid-binding protein; NA = not available; NAG = N-acetyl-β-D-glucosaminidase; NGAL = neutrophil gelatinase-associated lipocalin; PN = partial nephrectomy; PPRP = percentage of preserved renal parenchyma; RIFLE = risk, injury, failure, loss and end-stage kidney disease; RN = radical nephrectomy; SCr = serum creatinine.
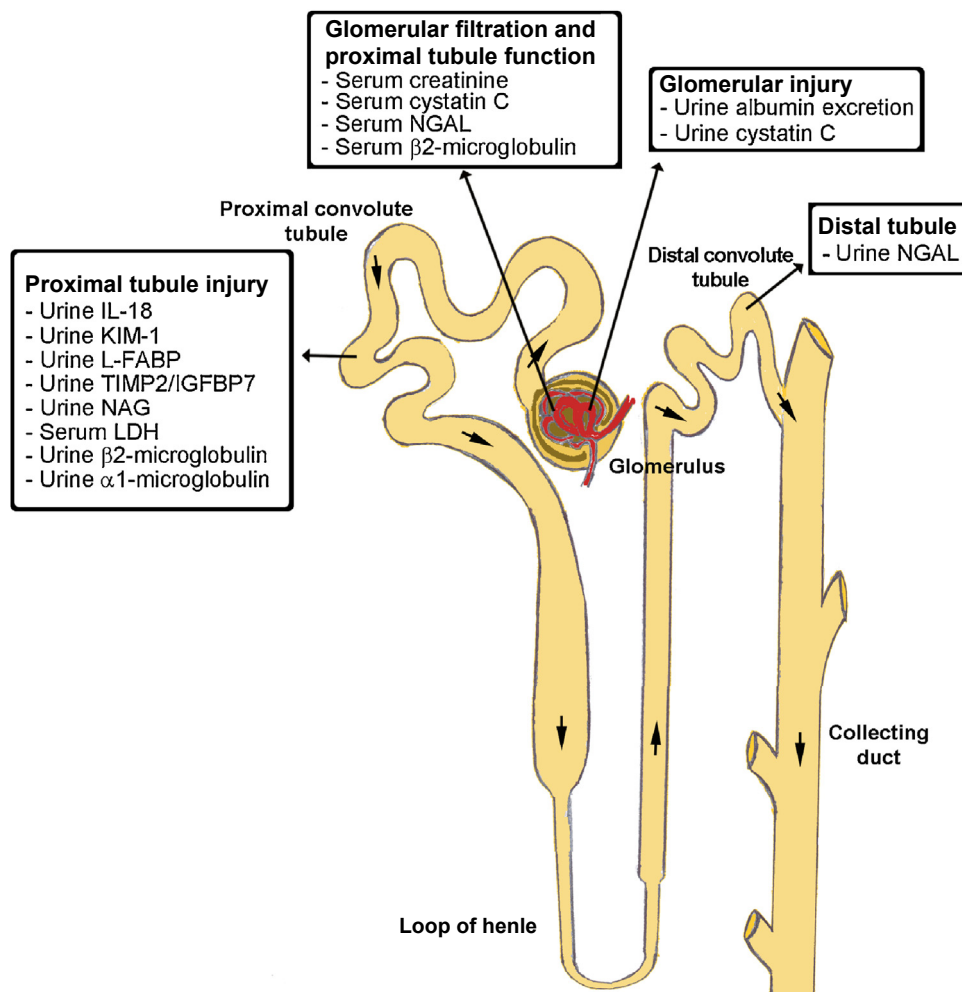
Fig. 1 – Investigated biomarkers of AKI in relation to the site of injury in the nephron. AKI = acute kidney injury; IL = interleukin; KIM–1 = Kidney Injury Molecule-1; LDH = lactase dehydrogenase; L-FABP = liver-type fatty acid–binding protein; NAG = N-acetyl-β-D-glucosaminidase; NGAL = neutrophil gelatinase–associated lipocalin.

magnitudes of the variation in biomarker value and the diagnosis of AKI.

Glomerular filtration rate (GFR) equations that are routinely used throughout medicine (Cockroft-Gault, MDRD, CKD-EPI) are not routinely used in the acute setting, and all the definitions of AKI are based on serum creatinine and urine output changes.

International guidelines and study groups adopted the following definitions criteria for AKI:

1. RIFLE [7]: serum creatinine >50% increase from baseline, and/or urine volume <0.5 ml/kg/h for 6 h
2. AKIN [8]: serum creatinine >50% increase or by 0.3 mg/dl from baseline in 48 h, and/or urine volume <0.5 ml/kg/h for 6 h
3. KDIGO [9]: serum creatinine >50% increase within the prior 7 d or by 0.3 mg/dl from baseline in 48 h, and/or urine volume <0.5 ml/kg/h for 6 h

Unfortunately, their adoption to clinical practice was found to be still insufficient as the majority of studies

referred exclusively to changes in serum creatinine, according to various thresholds and magnitudes. Therefore, based upon these limitations, for the present review, the predictive role of biomarkers for AKI was evaluated according to the respective definitions of AKI adopted by the studies.

2.3. Risk of bias

Based on the Cochrane risk of bias (RoB) tool, two reviewers (G.R. and A.C.) independently assessed the RoB for each included study [10]. Both RoB and applicability of the study cohort level were assessed through the validated Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) scoring system [11]. Four domains were scored: (1) *patient selection*, which describes the methods of patient selection and exclusion; (2) *index test*, which describes the tests performed and methodology; (3) *reference standard*, which describes the reference standard used and how it was conducted and interpreted; and (4) *flow and timing*, which describes the flow of patient inclusion and exclusion, and the interval between the index test and the reference
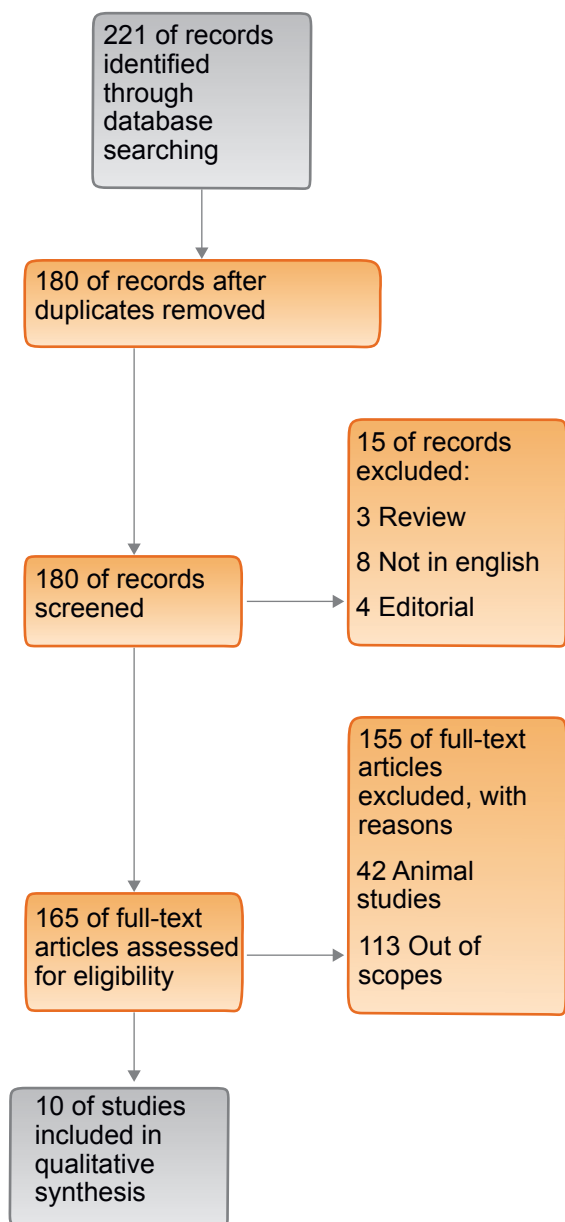
Fig. 2 – Study flow diagram according to CONSORT statement.

studies. All included studies are prospective, with the sole exception of a retrospective study [21] that analyzes a potential biomarker already present in clinical practice. Overall, there was a low RoB across all studies (Fig. 3), despite wide heterogeneity in cohorts and AKI definitions. Thirty-two additional papers were referenced in this review to (1) clarify the physiopathology of the markers, (2) explain their potential role in the clinical practice, and (3) introduce concepts such as "subclinical AKI" or "multifactorial etiology of AKI."

3.1.2. Characteristics of study populations

The pooled mean age of patients was 56.3 yr (standard deviation [SD]: ±4.9) and the pooled mean ischemia time in patients undergoing PN was 29.9 min (SD: ±8.3). Incidence of postoperative AKI was 26.7% (range: 9–58%).

It was found that most of the studies did not adopt any conventionally accepted definition of AKI, omitting the criterion of the urine output and relying on arbitrary thresholds of serum creatinine.

3.1.3. Biomarkers

3.1.3.1. NGAL. NGAL, a lipocalin protein involved in innate immunity, is produced by renal tubular cells in response to ischemic and toxic injury (Fig. 1), and its concentration in serum and urine increases from 8 to 24 h prior to the increase in serum creatinine [22]. NGAL has emerged as a promising noninvasive, sensitive, and early biomarker of AKI in several different settings, and is the most widely studied biomarker for AKI [23].

Five studies reported that NGAL increased after PN or RN in proportion to the amount of renal injury, according to a definition of AKI. NGAL was measured in the urine in four studies [12,14,19,20] and in both in three studies [15–17].
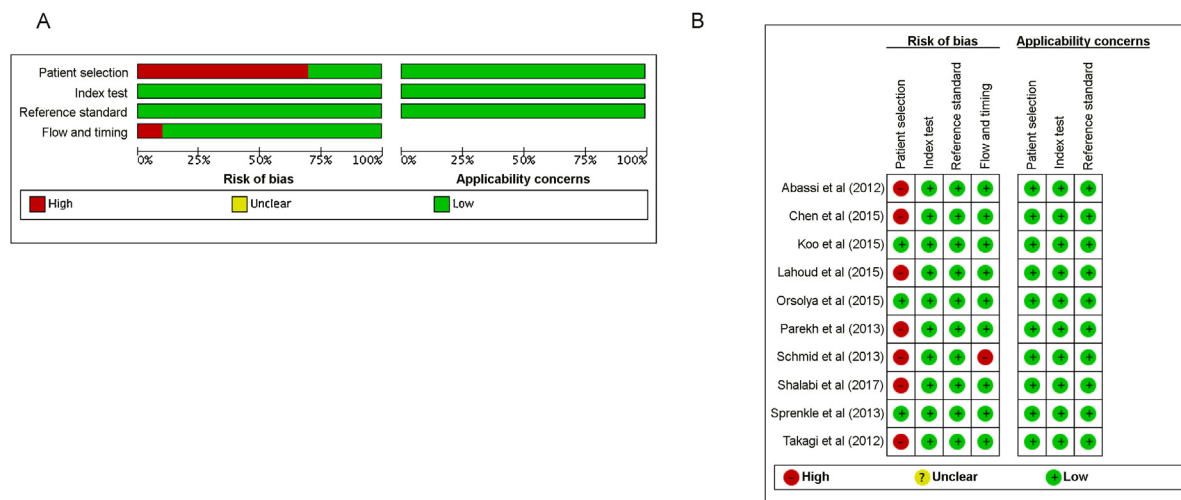
In three studies [12,15,19], postoperative levels of urinary NGAL were significantly increased in patients with AKI compared with patients without AKI, and correlated with ischemia. Regarding the timing of increase, urinary NGAL was augmented after 8 h following PN [12,15], but more precociously—3 h—in patients with further diagnosis of AKI, it was not associated with ischemia duration [14].

On the contrary, three studies [16,17,20], even confirming postoperative increase of urinary NGAL levels, failed to found an association with peak serum creatinine and ischemia time.

Furthermore, several studies did not find a significant increase in serum NGAL levels after laparoscopic [16] and open PN [15,17].

3.1.3.2. KIM-1. KIM-1 is a type I membrane protein expressed at very low levels in the normal kidney, but its expression in renal tubules (Fig. 1) increases under ischemia, demonstrating its biological plausibility as a marker of AKI [24]. KIM-1 was proved to be an early biomarker of AKI and to have a potential role in predicting long-term renal outcome [25].

In four studies, urinary KIM-1 levels were investigated in patients who underwent PN or RN [12,15,17,19]. All studies showed a postoperative KIM-1 rise and its subsequent decrease in all patients. Compared with patients without

standard. Each item was scored as "yes," "no," or "unclear." Any discrepancy was solved by a third reviewer (M.A.).

3. Evidence synthesis

3.1. Results

3.1.1. Quality of the studies

Among a total of 221 studies, 165 were assessed for eligibility and finally 10 publications were included in this systematic review [12–21]. Fig. 2 outlines the study selection process according to the PRISMA flow. Ultimately, 10 studies met the inclusion criteria recruiting a total of 728 patients. Table 1 provides the summary of all included

Fig. 3 – (A) Graph of risk of bias and applicability concerns: review authors' judgments about each domain presented as percentages across included studies. (B) Summary of risk of bias and applicability concerns: review authors' judgments about each domain for each included study.

AKI, urinary KIM-1 levels at 8 [12,19] and 24 h [17] were found to not have significantly increased. One study demonstrated that patients who developed postoperative AKI exhibited a higher percentage of increase from baseline in urinary KIM-1 after 8–24 h, as compared with patients with postoperative normal kidney function [15].

3.1.3.3. Cystatin C. Cystatin C is produced at a constant rate by all nucleated cells, and is freely filtered by the glomerulus and reabsorbed by the proximal tubule (Fig. 1). It is not secreted by renal tubules and does not vary with gender, race, weight, changes of muscle mass, and nutrition [26]. Serum cystatin C is a well-validated biomarker of GFR and may reveal AKI with more accuracy than creatinine [27].

The role of cystatin C as a predictor of AKI has been investigated in three studies [13,17,18] showing direct association with postoperative AKI. Elevated serum cystatin C levels were significantly correlated with the postoperative occurrence of AKI [10], and serum cystatin C at 24 h appeared to be superior to creatinine in predicting CKD development at 1-yr follow-up [15]. On the contrary, Parekh et al [17] argued that there was no correlation between the change in creatinine and the change in serum cystatin C at 24 h.

3.1.3.4. Albuminuria. Albuminuria is a sensitive marker for glomerular damage (Fig. 1), increasing after AKI in several settings of patients, but only limited studies have suggested the real utility as a biomarker for AKI. From experimental models, which were further corroborated in humans, albuminuria was described to increase as early as 4 h following injury only due to intrinsic renal causes (ischemia reperfusion, nephrotoxin, and rhabdomyolysis) and not in either prerenal (secondary to endotoxin) or postrenal (obstructive uropathy) conditions [28].

Only two studies described the role of albuminuria after PN [13,17], showing its poor role as an AKI biomarker. Both studies found that AKI-group patients had higher levels of preoperative albuminuria compared with the non-AKI-group, but albuminuria exhibited a poor predictive ability at postoperative 2 [17] and 24 h [13].

3.1.3.5. LDH. LDH is an enzyme that catalyzes the conversion of lactate to pyruvate, and the kidney is relatively rich in LDH. Serum LDH might be considered a biomarker of AKI because it is released when tubular cells are disordered and finds its way into the blood [29].

Postoperative LDH, measured 5 d after surgery, appeared as a predictor for renal insufficiency after open PN [21]. Although LDH does not appear to be a promising biomarker of AKI due to lack of specificity and its heterogeneous behavior in different tissues, it was tested only in a single study on patients who underwent PN or RN.

3.1.3.6. Other biomarkers. Liver-type fatty acid–binding protein (L-FABP), a cytoplasmic protein found in the renal proximal tubule, appeared as a promising biomarker because its serum and urinary concentrations were significantly higher in patients with ischemic and nephrotoxin-induced AKI [30].

N-acetyl-β-D-glucosaminidase (NAG) is an enzyme produced by the lysosomes of the renal proximal tubular cells. NAG might be a useful biomarker of AKI. Its increase in urine derives from tubular damage and occurs about 12 h before the rise in serum creatinine in a intensive care unit setting [31].

Interleukin-18 (IL-18) is an important mediator of tubular apoptosis, and its urinary concentrations were found to be significantly higher in patients with ischemic AKI, in several settings [32].

Several different biomarkers (serum L-FABP, serum and urinary beta 2-microglobulin, urinary alpha-1 microglobulin, urinary NAG, and urinary IL-18), which appeared to be promising biomarkers of AKI in different settings, were tested in

single studies on patients who underwent PN or RN, but they did not show any association with AKI and ischemia time [17]. They all had significant changes after surgery; however, the median increases of these novel biomarkers were modest only in comparison with changes in serum creatinine.

3.2. Discussion

After decades of being deemed reversible and a mere complication of severe illness, AKI has gained recognition as a serious contributor to short- and long-term morbidity and mortality.

Depending on the definition of AKI and surgical techniques adopted, data showed that AKI occurred in 13–47% of patients who had undergone RN and 9–41% of patients who had undergone PN (Table 1), suggesting that AKI remains a common clinical condition in this particular setting of patients. This figure is reasonably underestimated, considering that the majority of studies did not adhere to a rigorous definition of AKI but were based exclusively on serum creatinine levels, omitting the rate of cases in which AKI appears as a reduction in urine output.

Accumulating evidence supports the use of a nephron-sparing approach for clinically localized tumors to prevent or reduce the incidence of postoperative AKI and consequently the development of new-onset CKD [2,4]. Indeed, although several clinical factors may impact renal function after kidney surgery, preoperative CKD and RN (when compared with PN) are identified as independent predictors of postoperative AKI [33]. Although a rise in serum creatinine after RN is expected, often this is not a reflection of AKI (which should be considered an injured remaining kidney) but simply a loss of parenchymal volume. In other words, an acute increase in serum creatinine after PN was thought to be primarily due to functional parenchymal mass reduction and ischemia [2,34], but AKI, particularly in this setting, has a multifactorial etiology depending on ischemia-reperfusion injury, microembolization, inflammation and consequent endothelial injury [35], intraoperative hypotension and decreased renal perfusion pressure (eg, bleeding, anesthetics, and pneumoperitoneum) [36], hemodilution, and use of nephrotoxic drugs. However, the contribution of each of these factors is unknown, and this lack of knowledge is clinically relevant because some of the different causes underlying surgical renal insult are preventable or reversible and therefore their identification could be paramount.

The majority of the studies on AKI adopt serum creatinine as an indicator of renal damage although its limitations are well known, being influenced by age, body composition, and nutritional and fluid status (such as the dilutional effect of fluid overload and the use of diuretics) [37].

With this systematic review, we found that specific biomarkers could be useful for the prediction of postoperative AKI after renal surgery, as complementary rather than in competition with serum creatinine.

Renal biomarkers of AKI can suggest normal or impaired function of the kidney. Many novel urinary and serum biomarkers have been proposed for the prediction and early detection of AKI following PN or RN: NGAL, KIM-1, cystatin C, albuminuria, and LDH.

We found significant changes after renal surgery for most of the evaluated biomarkers, indicating that any renal damage provokes a prompt variation of these substances in serum or urine.

Based on the evidence reviewed (Table 1), serum cystatin C and urinary NGAL showed a significant correlation with serum creatinine rise postoperatively, emerging as potential noninvasive and early biomarkers of AKI in patients undergoing PN and RN. In this setting, both were elevated at earlier time points (3–24 h after the end of surgery) compared with serum creatinine (12–48 h after surgery) and were significantly correlated with the postoperative occurrence of AKI. Moreover, the former appeared to be superior to creatinine in predicting renal function at 1 yr follow-up [18], and the latter, historically considered the "troponin of the kidney," appeared to be the earliest biomarker in this setting, showing a remarkable increase, of up to 100-fold from baseline, within 2–8 h after surgery [12,15,16,19].

Conversely, all the other reviewed biomarkers had significant changes after surgery but did not correlate with peak serum creatinine.

As expected, urinary NGAL did not show a significant correlation with creatinine peak in patients undergoing RN [16,20]. This might suggest a potentially better application of the tubular biomarkers (biomarkers of renal damage) in the PN setting and of the biomarkers of GFR (biomarkers of nephron mass) such as cystatin C in the RN setting. However, tubular biomarkers might also be useful in detecting subclinical damage in the contralateral kidney after RN. In fact, loss of parenchymal volume leads to a change in creatinine independent of the injury to the remaining kidney.

Besides the volume of preserved renal parenchyma, type and duration of ischemia during PN remain one of the most important modifiable factors for renal functional outcome. The impact of renal ischemia-reperfusion injury on renal function was studied with different biomarkers (Table 1), which did not show any correlation with ischemia type and duration [14,17,20,21], with the exception of urinary NGAL that showed conflicting results [12,14,15,20]. This might be explained by a selection bias: patients were younger and had fewer comorbidities than in real clinical practice. Moreover, as recently demonstrated by Parekh et al [17] and reviewed by Mir et al [37], human kidneys can safely tolerate 30 min of controlled clamp ischemia or even more (depending on concurrent comorbidities), with only mild structural changes and no acute functional loss.

Novel biomarkers can predict early damage before creatinine rise, detect mild renal damage not identified by creatinine (subclinical AKI) [38,39], and therefore be useful for the diagnosis of AKI within the context of CKD. This could explain why biomarker levels after surgery failed to reveal an association with peak serum creatinine in several studies that we previously analyzed, suggesting that it would be better to compare biomarker levels after surgery with new-onset or worsening CKD at a long-term follow-up. Despite heterogeneity in the AKI definition adopted by

different studies, the lack of correlation between AKI and biomarker variations suggests that serum creatinine is not sufficiently adequate to depict (mild to moderate) renal injury and that the definition of AKI should be redefined by the introduction of novel biomarkers into clinical practice and maybe also accounting for lost parenchymal volume [40].

Although novel biomarkers can address diagnostic delay in AKI, further research is needed to advance biomarkers from the laboratory to bedside.

Recently, the US Food and Drug Administration approved the first AKI point-of-care biomarker device NephroCheck. It measures urinary levels of TIMP-2 and IGFBP7, which are biomarkers of cell cycle arrest in tubular epithelial cells, a key mechanism implicated in AKI. A recent meta-analysis demonstrated that urine [TIMP-2]*[IGFBP7] is a promising candidate for early detection of AKI in different settings [41], but it has never been tested in patients undergoing PN and RN.

Novel biomarkers need to prove their clinical applicability, accuracy, and cost effectiveness prior to implementation into clinical practice, and further large-scale prospective cohort studies are required.

With the application of new AKI definition criteria and available AKI biomarkers, a more accurate evaluation of the real incidence of kidney dysfunction in patients undergoing PN and RN could be documented.

Limitations of this study include the lack of diagnostic meta-analysis aiming to assess the accuracy of current biomarkers in predicting AKI.

Perhaps in the future, the combination of biomarkers of kidney damage (NGAL, KIM-1, NephroCheck, albuminuria) and kidney function (creatinine or cystatin C, and urine output), rather than a single biomarker (which represents a single biological process), will be needed to facilitate the diagnosis of AKI and positively improve a patient's long-term renal functional outcomes.

4. Conclusions

In this systematic review of the literature, we have highlighted the usefulness of biomarkers in predicting AKI after PN or RN. In an effort to move away from the sole use of creatinine in diagnosing renal injury, the paradigms proposed in this review might lead physicians to further investigate the role of serum cystatin C and urinary NGAL within clinical setting in order to better personalize patient care. Surgeons are in need of a better definition of AKI more related to a highly sensitive and early biomarker. Large clinical studies are needed before defining the role of these biomarkers of AKI in urological patients. Novel biomarkers have to prove their clinical applicability, accuracy, and cost effectiveness prior to implementation into clinical practice.

References

[1] Schmid M, Krishna N, Ravi P, et al. Trends of acute kidney injury after radical or partial nephrectomy for renal cell carcinoma. Urol Oncol 2016;34(293):e1–10.

[2] Cho A, Lee JE, Kwon GY, et al. Post-operative acute kidney injury in patients with renal cell carcinoma is a potent risk factor for new-onset chronic kidney disease after radical nephrectomy. Nephrol Dial Transplant 2011;26:3496–501.

[3] Campbell SC, Novick AC, Streem SB, Klein E, Licht M. Complications of nephron sparing surgery for renal tumors. J Urol 1994;151:1177–80.

[4] Patel HD, Pierorazio PM, Johnson MH, et al. Renal functional outcomes after surgery, ablation, and active surveillance of localized renal tumors: a systematic review and meta-analysis. Clin J Am Soc Nephrol 2017;12:1057–69.

[5] Chen H, Busse LW. Novel therapies for acute kidney injury. Kidney Int Rep 2017;2:785–99.

[6] Andreucci M, Faga T, Pisani A, Perticone M, Michael A. The ischemic/nephrotoxic acute kidney injury and the use of renal biomarkers in clinical practice. Eur J Intern Med 2017;39:1–8.

[7] Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P. Acute dialysis quality initiative workgroup acute renal failure—definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. Crit Care 2004;8:R204–12.

[8] Mehta RL, Kellum JA, Shah SV, et al. Acute kidney injury network: report of an initiative to improve outcomes in acute kidney injury. Crit Care 2007;11:R31.

[9] KDIGO. Clinical practice guideline for acute kidney injury. Kidney Int Suppl 2012;2:1–141.

[10] Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011;343:d5928.

[11] Whiting PF, Rutjes AW, Westwood ME, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med 2011;155:529–36.

[12] Abassi Z, Shalabi A, Sohotnik R, et al. Urinary NGAL and KIM-1: biomarkers for assessment of acute ischemic kidney injury following nephron sparing surgery. J Urol 2013;189:1559–66.

[13] Chen J, Lin J, Lin C. Serum and urinary biomarkers for predicting acute kidney injury after partial nephrectomy. Clin Invest Med 2015;38:E82–9.

[14] Koo KC, Hong JH, Lee HS, et al. Accuracy of urinary neutrophil gelatinase-associated lipocalin in quantifying acute kidney injury after partial nephrectomy in patients with normal contralateral kidney. PLoS One 2015;10:e0133675.

[15] Lahoud Y, Hussein O, Shalabi A, et al. Effects of phosphodiesterase-5 inhibitor on ischemic kidney injury during nephron sparing surgery: quantitative assessment by NGAL and KIM-1. World J Urol 2015;33:2053–62.

[16] Mihaly O, Bolboaca SD, Rahaian R, et al. Accuracy of neutrophil gelatinase-associated lipocalin in detecting acute kidney injury after urogenital robotic assisted laparoscopic surgery under general anesthesia. Appl Med Inform 2012;30:47–56.

[17] Parekh DJ, Weinberg JM, Ercole B, et al. Tolerance of the human kidney to isolated controlled ischemia. J Am Soc Nephrol 2013;24:506–17.

[18] Schmid M, Abd-El-Barr AE, Gandaglia G, et al. Predictors of 30-day acute kidney injury following radical and partial nephrectomy for renal cell carcinoma. Urol Oncol 2014;32:1259–66.

[19] Shalabi A, Nativ O, Sumri M, et al. Impact of pneumoperitoneum on the post-operative renal function and level of acute kidney injury markers: comparison between laparoscopic and open nephrectomy. Int Arch Urol Complications 2017;3:1–6.

[20] Sprenkle PC, Wren J, Maschino AC, et al. Urine neutrophil gelatinase-associated lipocalin as a marker of acute kidney injury after kidney surgery. J Urol 2013;190:159–64.

[21] Takagi T, Kondo T, Iizuka J, et al. Predictors for postoperative renal function after open partial nephrectomy: including postoperative biomarkers. Int J Urol 2012;19:823–8.

[22] Mårtensson J, Bellomo R. The rise and fall of NGAL in acute kidney injury. Blood Purif 2014;37:304–10.

[23] Ronco C, Legrand M, Goldstein SL, et al. Neutrophil gelatinase-associated lipocalin: ready for routine clinical use? An international perspective. Blood Purif 2014;37:271–85.

[24] Ichimura T, Asseldonk EJ, Humphreys BD, et al. Kidney injury molecule-1 is a phosphatidylserine receptor that confers a phagocytic phenotype on epithelial cells. J Clin Invest 2008;118:1657–68.

[25] Yin C, Wang N. Kidney injury molecule-1 in kidney disease. Ren Fail 2016;38:1567–73.

[26] Kaseda R, Iino N, Hosojima M, et al. Megalin-mediated endocytosis of cystatin C in proximal tubule cells. Biochem Biophys Res Commun 2007;357:1130–4.

[27] Zhang Z, Lu B, Sheng X, Jin N. Cystatin C in prediction of acute kidney injury: a systemic review and meta-analysis. Am J Kidney Dis 2011;58:356–65.

[28] Bolisetty S, Agarwal A. Urine albumin as a biomarker in acute kidney injury. Am J Physiol Renal Physiol 2011;300:F626–7.

[29] Zager RA, Johnson AC, Becker K. Renal cortical lactate dehydrogenase: a useful, accurate, quantitative marker of in vivo tubular injury and acute renal failure. PLoS One 2013;8:e66776.

[30] Yamamoto T, Noiri E, Ono Y, et al. Renal L-type fatty acid–binding protein in acute ischemic injury. J Am Soc Nephrol 2007;18:2894–902.

[31] Westhuyzen J, Endre ZH, Reece G, Reith DM, Saltissi D, Morgan TJ. Measurement of tubular enzymuria facilitates early detection of acute renal impairment in the intensive care unit. Nephrol Dial Transplant 2003;18:543–51.

[32] Parikh CR, Jani A, Melnikov VY, Faubel S, Edelstein CL. Urinary interleukin-18 is a marker of human acute tubular necrosis. Am J Kidney Dis 2004;43:405–14.

[33] Lane BR, Babineau DC, Poggio ED, et al. Factors predicting renal functional outcome after partial nephrectomy. J Urol 2008;180:2363–9.

[34] Thomas AA, Demirjian S, Lane BR, et al. Acute kidney injury: novel biomarkers and potential utility for patient care in urology. Urology 2011;77:5–11.

[35] Becker F, Van Poppel H, Hakenberg OW, et al. Assessing the impact of ischaemia time during partial nephrectomy. Eur Urol 2009;56:625–34.

[36] Walsh M, Devereaux PJ, Garg AX, et al. Relationship between intraoperative mean arterial pressure and clinical outcomes after noncardiac surgery: toward an empirical definition of hypotension. Anesthesiology 2013;119:507–15.

[37] Mir MC, Pavan N, Parekh DJ. Current paradigm for ischemia in kidney surgery. J Urol 2016;195:1655–63.

[38] Haase M, Kellum JA, Ronco C. Subclinical AKI—an emerging syndrome with important consequences. Nat Rev Nephrol 2012;8:735–9.

[39] Huen SC, Parikh CR. Molecular phenotyping of clinical AKI with novel urinary biomarkers. Am J Physiol Renal Physiol 2015;309:F406–13.

[40] Zhang Z, Zhao J, Dong W, et al. Acute kidney injury after partial nephrectomy: role of parenchymal mass reduction and ischemia and impact on subsequent functional recovery. Eur Urol 2016;69:745–52.

[41] Liu C, Lu X, Mao Z, et al. The diagnostic accuracy of urinary [TIMP-2]•[IGFBP7] for acute kidney injury in adults: a PRISMA-compliant meta-analysis. Medicine (Baltimore) 2017;96:e7484.