Review Article

Urinary biomarkers in pelvic-ureteric junction obstruction: a systematic review

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Abstract: Antenatal hydronephrosis is a common finding detected on prenatal ultrasound. Although hydronephrosis will spontaneously resolve in the majority of newborns, there is a significant amount of cases that will worsen with the risk of a progressive and permanent loss of renal function. There is an increasing concern among experts that the current criteria for evaluation of clinically significant obstructions are limited. Our aim is to provide a systematic review of the available literature on biomarkers of renal injury, potential targets for diagnosis and prognosis of children with hydronephrosis. The main search was conducted in the electronic databases from inception through March 2019 using various combinations of the keywords: pelvic-ureteric [All Fields] AND junction [All Fields] AND obstruction [All Fields] AND "biomarkers" [MeSH Terms] OR "biomarkers" [All Fields] OR "biomarker" [All Fields]. To broaden the research, additional articles were identified through hand-searching review of the references reported in each study previously selected. Histopathological studies, studies with no control group or with participants suffering from concomitant urological diseases and articles published in language other than English were excluded. Data on study design, sample size, average patient age, hydronephrosis definition used, surgical indication, duration and pattern of follow-up, details on biomarker studied, diagnostic test characteristics, area under the curve (AUC) on receiver operating characteristic (ROC) analysis with the best cut-off (BCO) values, sensitivity, specificity and outcomes were all collected. 38 articles analysing 41 biomarkers were selected. The most frequent proteins investigated were neutrophil gelatinase-associated lipocalin (NGAL) (n=9; 23.7%), monocyte chemotactic peptide-1 (MCP1) (n=8; 21.1%), transforming growth factor β1 (TGFβ1) (n=7; 18.4%), epidermal growth factor (EGF) (n=6; 15.8%) and kidney injury molecule 1 (KIM 1) (n=6; 15.8%). Twenty-seven (71.1%) studies evaluated the effect of pyeloplasty on voided urine biomarker concentrations, comparing their values before and after surgery. Twelve (31.6%) studies investigated the correlation between preoperative biomarker concentration and the anterior posterior renal pelvis diameter (DAP) while 20 (52.6%) studies investigated the correlation between preoperative biomarker concentration with the split renal function (SRF) measured on nuclear medicine assessments. ROC curves were used to investigate the performance of urinary biomarkers in the total patient data set in 27 (71.1%) studies. Some biomarkers offer promising results. However, a critic analysis of the published studies demonstrates bias and lack of consistency suggesting that larger multicentre and carefully designed prospective studies are still needed to evaluate the clinical usefulness of urinary biomarkers in the diagnosis and follow-up of children with congenital obstructive hydronephrosis.

Keywords: Pelvic-ureteric junction obstruction (PUJO); biomarkers; hydronephrosis; kidney injury

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Introduction

One of the most common causes of renal failure in infants and children is obstructive nephropathy due to congenital hydronephrosis secondary to pelvic-ureteric junction obstruction (PUJO) (1,2). Despite extensive clinical and experimental studies have been undergone over the past decades, fundamental issues regarding the evaluation and management of children with upper urinary tract obstruction remain unsolved.

It is known that the majority of the children with antenatally diagnosed hydronephrosis will have a spontaneous resolution of the dilatation. However, there is a significant amount of cases that will worsen with the risk of a progressive and permanent loss of renal function. The main goal of paediatric urologists is the preservation of kidney function through early selection of patients who will require surgical intervention as opposed to those who have chances to improve spontaneously.

The classic diagnostic tools for investigation of children with upper tract renal obstruction include ultrasound scans, nuclear medicine assessments [(dimercaptosuccinic acid) scan and technetium-99m (Tc-99m DMSA) mercaptoacetyltriglycine (MAG3) renal studies], contrast studies such as micturating cystourethrogram (MCUG) and conventional markers of renal function (such as serum creatinine).

However, these tests are not always adequate predictors for disease progression, particularly for border-line cases. Commonly indication for surgery is currently based on: (I) half-time of the elimination phase (T1/2) of diuretic renogram >15–20 minutes, (II) differential renal function (DRF) less than 40%, (III) deteriorating renal function (more than 5% in successive radionuclide scans), (IV) progressive thinning of the renal cortex with or without compensatory hypertrophy of the other kidney (V) frequent pyelonephritis (VI) significant grade hydronephrosis, usually greater than 20 mm (VII) other symptoms such as hypertension, kidney stones, flank pain (3).

However, there is an increasing concern among experts that the aforementioned criteria can't timely identify patients who need surgery from those who can be managed conservatively. The use of urinary biomarkers has been advocated, which could discriminate patients whose renal function will deteriorate from those who will spontaneously improve at an early stage, preventing at the same time unnecessary surgeries. Recently, proteomic has become a very important diagnostic and prognostic tool in the armamentarium of clinicians. Evaluating proteins using proteomic technologies has the ability to increase the understanding and elucidate the cellular and the molecular basis of a particular disorder. In addition, the proteins analysed could be used to identify and quantify a disease at an early stage of occurrence. The etiopathogenesis of renal injury and progression of renal disease in obstructive nephropathy has been well described. It consists of a sequence of cellular and molecular events which includes renal hemodynamic responses, macrophage infiltration of the interstitium, tubular dilatation and apoptosis, accumulation of interstitial fibroblasts through proliferation of resident fibroblasts and epithelial-mesenchymal transformation of renal tubular cells. This process is under the influence of multiple enzymes, cytokines, chemokines, growth factors, signaling molecules and genes (4). Using proteomic analysis, in the last years several attempts have been made to evaluate molecules that could be utilized as potential biomarkers in PUJO in children, most of them concluding to promising results. We have performed an up-to-date systematic review of the literature on biomarkers of renal injury and dysfunction, potential targets for diagnosis, prognosis and treatment of children with PUJO.

Methods

This review was performed according to the Preferred Reporting Items for Systematic Reviews and Metanalysis Statement (http://www.prisma-statement.org/). In order to identify eligible studies, a broad search was conducted in the electronic database MEDLINE from inception through March 2019 using various combinations of keywords such as pelvic-ureteric [All Fields] AND junction [All Fields] AND obstruction [All Fields] AND "biomarkers" [MeSH Terms] OR "biomarkers" [All Fields] OR "biomarker" [All Fields]. To broaden the research, additional records were identified through hand-searching review of the references reported in each article previously selected.

Selection was limited to original articles in English language presenting promising protein biomarkers of PUJO in children. Two independent reviewers (Irene Paraboschi and Massimo Garriboli) performed data extraction and quality assessment. Any disagreement was resolved by consensus or by arbitration of a third author (Guglielmo Mantica) not involved in the initial procedure.

An electronic schedule (Microsoft Excel 2007, Redmond, WA, USA) was pre-established listing authors, article title, journal, year of publication, study period, study design,

sample size, average age, hydronephrosis definition used, surgical indication, duration and pattern of follow-up, details on biomarker studied, diagnostic test characteristics, area under the curve (AUC) on receiver operating characteristic (ROC) analysis with best cut-off (BCO) values, sensitivity, specificity and outcomes.

The eligibility for the systematic review were studies of any design that reported interleukin 6 (IL6), neutrophil gelatinase-associated lipocalin (NGAL), monocyte chemotactic peptide-1 (MCP1), transforming growth factor β1 (TGFβ1), carbohydrate antigen 19.9 (CA19.9), kidney injury molecule 1 (KIM1), glutathione S-transferases (GSTs), antimicrobial peptides (AMPs), such as B defense 1 (BD1), cathelicidin (LL37), hepatocarcinoma-intestine-pancreas/pancreatitis-associated protein (HIP/PAP), and human a defensin 5 (HD5), caspase 3 enzyme, tumor necrosis factor α (TNFα), thioredoxin (Trx), proximal tubule metallopeptidases (such as CD10, CD13, CD26), intercellular adhesion molecule 1 (ICAM1), lysosomal exoglycosidases (such as HEX A, HEX B, FUC, GAL, MAN, GLU), epidermal growth factor (EGF), emmprin, matrix metalloproteinase 9 (MMP9), tissue inhibitor of metalloproteinase 1 (TIMP1), procollagen III aminoterminal propeptide (PIIINP), regulated on activation, normal T cell expressed and secreted (RANTES), sFas/Apo-1 (CD95), angiotensinogen (AGT), macrophage inflammatory protein 1a (MIP1a), interferon-γ-inducible protein-10 (IP10), osteopontin (OPN), cystatin C (CyC), β2microglobulin (β2M), heme oxygenase 1 (HO1), N-acetyl-β-D-glucosaminidase (NAG), alkaline phosphatase (ALP), γ-glutamyl transferase (GGT), endothelin 1 (ET1), semaphorin-3A (SEMA3A), netrin-1, liver-type fatty acid-binding proteins (L-FABP) in urine samples of children (until 18 years old) with unilateral or bilateral congenital PUJO compared to healthy controls or to children with dilated but not obstructed kidneys.

Histopathological studies were excluded from the systematic reviews as well as large scale urinary proteome analyses carried out through liquid chromatography coupled to tandem mass spectrometry (HPLC-MS/MS) or by mean high throughput techniques as matrice assisted laser desorption ionization or surface enhanced laser desorption ionization mass spectrometry (MALDI/SELDI-MS). Studies with no control group, studies with participants suffering from concomitant urological diseases and studies published in language other than English were also excluded.

Due to the heterogeneity of studies and especially the very small number of studies referring to the same biomarker a meta-analysis of the available data was deemed unfeasible.

Results

Out of 79 studies that were initially identified from the main search and through hand-searching review 40 were excluded: 28 were excluded on a title basis, 12 were excluded on abstract basis. Thirty-nine studies were evaluated on a full-text basis. Out of them, 1 had to be excluded due to inappropriate study population age, leaving in the end 38 studies that have been included in this review.

As shown in Prisma flow diagram (*Figure 1*), 8 articles were excluded because based on large scale urinary proteome analysis, 3 articles because they were written in language other than in English, 11 articles because they only reviewed previous studies, 14 articles because they did not analyse urinary protein biomarkers, 3 articles because they did not refer to paediatric age and 2 articles because they were systematic reviews. *Table 1* summarized data of the 38 studies published between November 1997 and October 2018. Out of the 38 studies included in this systematic review, all (100%) searched for urine biomarkers and 5 (13.2%) (7,12,18,22,34), included also serum samples. Thirty-two (84.2%) studies considered only patients with unilateral PUJO while 6 (15.8%) included also patients with bilateral obstruction (5,6,20,21,33,35). The quantitative urine protein analysis was performed using commercially available human sandwich enzyme-linked immunosorbent assay (ELISA) kits in 32 (84.2%) studies. Fourteen (36.8%) studies compared patients undergoing pyeloplasty [surgical group (SG)] with patients with mild non-obstructive dilatation not requiring surgery [non-surgical group (NSG)] and healthy children [reference group (RG)] (9,10, 14-18,20,22,27,29,31-33). Seven (18.4%) articles analysed urine biomarker concentrations in patients undergoing surgery (SG) and related them with patients conservatively treated (NSG) (6,19,21,28,36,37,41). Thirteen (34.2%) studies reported the comparison between surgical patients (SG) and healthy subjects (RG) (8,11,13,24-26,30,34,35, 38-40,42). Four (10.5%) articles compared patients with PUJO with healthy children (RG) without differentiating in the former group those who required surgery (5,7,12,23). Twenty-two (57.9%) studies evaluated the effect of pyeloplasty on voided urine biomarker concentrations, comparing their values before and after surgery (9,11, 14-16,18,22,24,25,27-32,34,35,37-39,41,42). Twelve (30.8%)

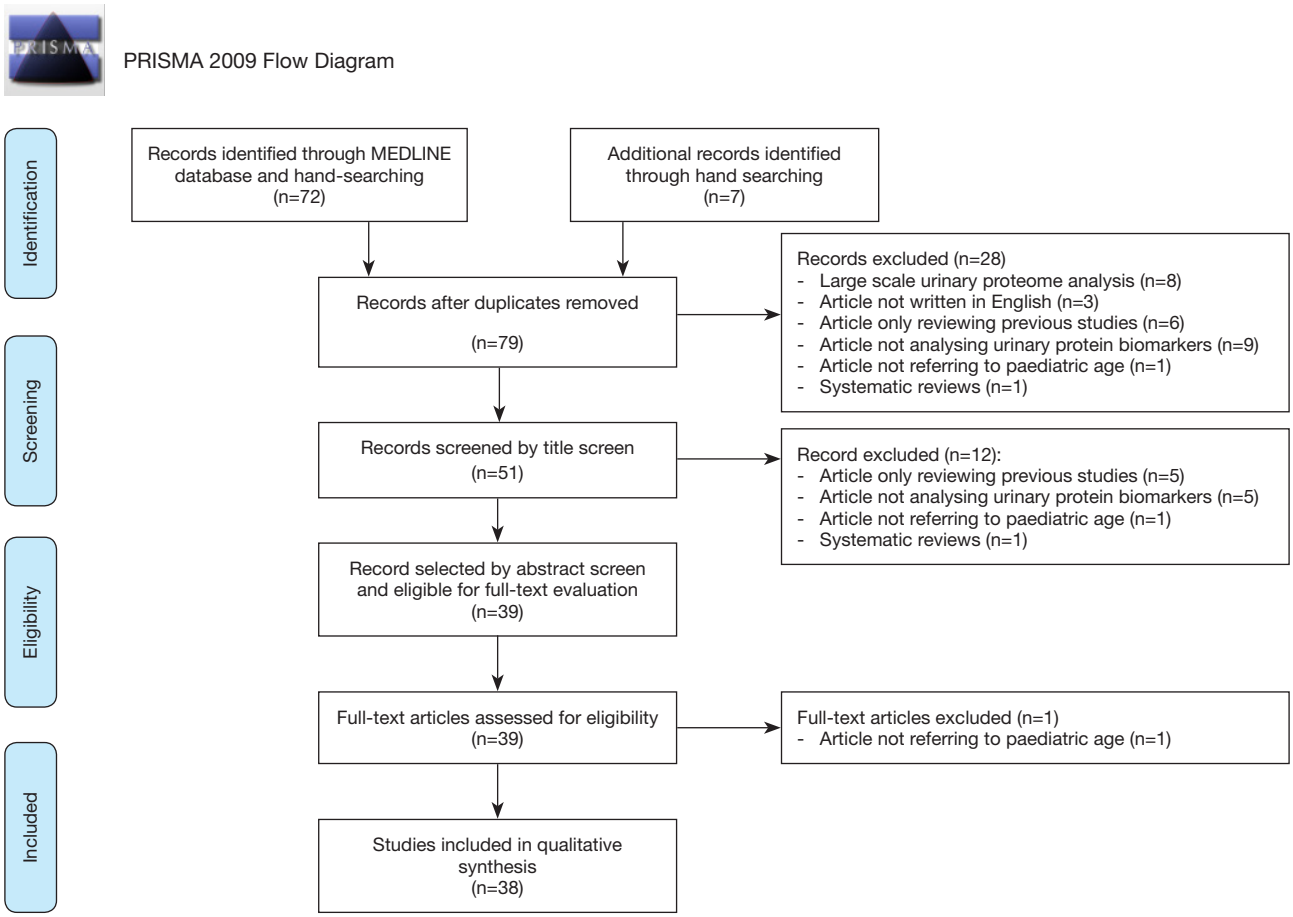

Figure 1 Prisma flowchart.

studies investigated the correlation between preoperative biomarker concentration with the anterior posterior renal pelvis diameter (DAP) (9,12,14,16,18,22,23,25,27,30-32) while 20 (52.6%) studies investigated the correlation between preoperative biomarker concentration with the split renal function (SRF) evaluated on nuclear medicine assessments (8,9,12-14,16,18,19,22,25-32,39,41,42). ROC curves were used to investigate the performance of urinary biomarkers in the total patient data set in 21 (55.3%) studies (5-9,14-22,24,27-32). *Table 2* summarized the results of the 38 articles classified them according to the type of urinary biomarker analysed.

NGAL

Preoperative urinary NGAL levels in surgical PUJO patients significantly differed from healthy controls in nine studies (5,7,8,13,15,17,26,30,32), and from dilated non-obstructed patients in two studies (17,32).

TGFβ1

Preoperative TGFβ1 levels in surgical PUJO patients were significantly higher than in healthy control group in 3 studies (23,35,39) while Palmer *et al.* (40) did not identify any significant difference. Preoperative TGFβ1 levels in surgical PUJO patients were significantly higher than in patients with mild non-obstructive hydronephrosis in the study of El-Sherbiny *et al.* (41).

A minority of studies performed a ROC analysis to define the diagnostic profile of TGFβ1. In the series reported by El-Sherbiny *et al.* (41) mean bladder TGFβ1 value 3 months after surgery showed a trend towards a decrease, albeit still insignificant. Conversely postoperative mean TGFβ1 concentration was significantly lower than the preoperative value according to Sager *et al.* (35) and Taha *et al.* (39).

Table 1 Articles on paediatric urinary biomarkers of PUJO

Reference	Year	No. of participants	Age of SG	Laterality	Urinary source	Biomarker	Method	SG pre op *vs.* SG post op	SG *vs.* NSG	SG *vs.* RG	Correlation with APD	Correlation with SRF
Yu *et al*. (5)	2019	PUJO: n=17; RG: n=17	ND	Unilateral: n=12; bilateral: n=5	Bladder	IL6; LCN2; MCP1; TGFβ1	ELISA	ND	ND	0.0073; 0.0004; 0.0005; NS	ND	ND
Nabavizadeh *et al*. (6)	2019	SG early: n=34; SG delayed: n=24; NSG: n=54	Mean (standard deviation): 30.0 (±8.9) mo	Unilateral: n=33; bilateral: n=1	Bladder	CA19.9	Chemiluminescence assays	ND	<0.001	ND	ND	ND
Bienias *et al*. (7)	2018	PUJO: n=45; RG: n=21	Median [range]: 11.0 [2–17] yrs	Unilateral: n=45	Bladder	α-GST; Π-GST; NGAL; KIM1	ELISA	ND	ND	ND	ND	ND
Gupta *et al*. (8)	2018	SG: n=30; RG: n=15	Mean (range): 4.7 (0.3–18.4) yrs	Unilateral: n=30	Bladder	BD1; NGAL; LL37; HIP/PAP; HD5	ELISA	ND	ND	0.0152; 0.0009; 0.0007; 0.0461; 0.1007	ND	NS
Li *et al*. (9)	2018	SG: n=42; NSG: n=42; RG: n=44	Median (range): 2.48 (0.17–16.9) yrs	Unilateral: n=42	Bladder; pelvis	Semaphorin-3A; netrin-1	ELISA	ND; <0.01	<0.01;<0.01	<0.01; <0.01	NS; NS	<0.01; <0.01
Sadeghi-Bojd *et al*. (10)	2018	SG: n=20; NSG: n=20; RG: n=30	Mean (standard deviation): 23.5 (±21.79) mo	Unilateral: n=20	Bladder	MCP1	ELISA	ND	0.005	0.001	ND	ND
Shirazi *et al*. (11)	2017	SG: n=31; RG: n=33	Mean (standard deviation): 22.44 (±20.52) mo	Unilateral: n=31	Bladder; pelvis	TNFα; caspase 3	ELISA	<0.01; <0.01	ND	<0.001; <0.001	ND	ND
Xu *et al*. (12)	2017	PUJO: n=156; RG: n=80	Median: 2.2 yrs	Unilateral: n=156	Bladder	Trx	ELISA	ND	ND	<0.001	<0.001	<0.001
Gerber *et al*. (13)	2016	SG: n=12; RG: n=12	Median [range]: 42 [4–240] mo	Unilateral: n=12	Bladder	NGAL; KIM1; CD10; CD13; CD26	ELISA	ND	ND	0.932; 0.799; 0.002; 0.024; 0.007	ND	NS
Taranta-Janusz *et al*. (14)	2016	SG: n=29; NSG: n=23; RG: n=19	Median (range): 1.75 yrs (1 wk–16.5 yrs)	Unilateral: n=29	Bladder	ICAM1	ELISA	NS	<0.05	<0.001	<0.001	<0.05
Karakuş *et al*. (15)	2016	SG: n=13; NSG: n=14; RG: n=9	Median [range]: 12 [2–56] mo	Unilateral: n=13	Bladder	NGAL; CyC; IP10; MCP1; KIM1	ELISA	Significant; NS; Significant; Significant; Significant	NS; NS; 0.038; 0.037; NS	0.032; NS; 0.024; 0.002; 0.001	ND	ND
Taranta-Janusz *et al*. (16)	2015	SG: n=16; NSG: n=16; RG: n=42	4.45 yrs (±4.66 yrs) (mean)	Unilateral: n=16	Bladder	HEX; HEX A; HEX B; FUC; GAL; MAN; GLU	Szajda-modified Marciniak method	<0.01	NS; <0.01; NS; NS; NS; NS; NS	<0.01; <0.01; <0.01; <0.01; <0.01; <0.01; <0.01	NS	NS
Noyan *et al*. (17)	2015	SG: n=26; NSG: n=36; RG: n=20	Median [range]: 21 [1–48] mo	Unilateral: n=26	Bladder	NGAL; KIM1; FABP	Micro ELISA	ND	<0.05;NS; NS	<0.05; NS; NS	ND	ND
Atar *et al*. (18)	2015	SG: n=17; NSG: n=17; RG: n=21	Mean (standard deviation): 15.3 (±14.6) mo	Unilateral: n=17	Bladder	CA19.9	ELISA	0.039	0.007	0.001	NS	0.046
Tian *et al*. (19)	2015	SG: n=15; NSG: n=25	ND	Unilateral: n=15	Bladder	Emmprin; MMP9; TIMP1	ELISA	ND	<0.0001; <0.05; <0.05	ND	ND	NS; 0.0012; NS
Mohammadjafari *et al*. (20)	2014	SG: n=24; NSG: n=18; RG: n=17	ND	Unilateral: n=18; bilateral: n=6	Bladder	EGF; KIM1	ELISA	ND	0.016; 0.015	ND	ND	ND
Mohammadjafari *et al*. (21)	2014	SG: n=24; NSG: n=18	Mean: 4.24 mo	Unilateral: n=18; bilateral: n=6	Bladder	ET1; MCP1; NAG	ELISA	ND	NS; 0.012; NS	ND	ND	ND
Wen *et al*. (22)	2014	SG: n=29; NSG: n=30; RG: n=30	Median (range): 2.2 (0.21–17) yrs	Unilateral: n=29	Bladder; pelvis	PIIINP	ELISA	<0.01	<0.01	<0.01	NS	<0.05

Table 1 (*continued*)

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Reference	Year	No. of participants	Age of SG	Laterality	Urinary source	Biomarker	Method	SG pre op *vs.* SG post op	SG *vs.* NSG	SG *vs.* RG	Correlation with APD	Correlation with SRF
Merrikhi *et al*. (23)	2014	PUJO: n=25; RG: n=25	Mean (standard deviation): 7.4 (±4.5) yrs	Unilateral: n=25	Bladder	TGFβ1	ELISA	ND	ND	0.001	NS	ND
Madsen *et al*. (24)	2013	SG: n=28; RG: n=13	Median (range): 8.1 (3.5–15) yrs	Unilateral: n=28	Bladder; pelvis	EGF; MCP1; MIP1A; IP10; CCL5/RANTES	ELISA	NS; NS; 0.0001; 0.0001; 0.0001	ND	0.012; 0.005; 0.0001; 0.1610; 0.3959	ND	ND
Gawłowska-Marciniak *et al*. (25)	2013	SG: n=45; RG: n=25	Mean (standard deviation): 8.4 (±5.66) yrs	Unilateral: n=45	Bladder; pelvis	TGFB1; CCL5/RANTES; sFas/Apo-1	ELISA	<0.05 (younger); <0.05 (older); <0.05 (younger); <0.05 (adolescent); <0.05 (younger); <0.05 (older)	ND	<0.05 (older); <0.05 (adolescent); <0.05 (younger); <0.05 (older); <0.05 (younger); <0.05 (older); <0.05 (adolescent)	NS	NS
Cost *et al*. (26)	2013	SG: n=25; RG: n=11	Median (range): 1.62 (0.12–18.7) yrs	Unilateral: n=25	Bladder; pelvis	NGAL	ELISA	ND	ND	0.004	ND	0.004
Taranta-Janusz *et al*. (27)	2013	SG: n=31; NSG: n=20; RG: n=19	Mean (standard deviation): 3.2 (±4.3) yrs	Unilateral: n=31	Bladder	AGT	ELISA	NS	<0.01	<0.01	NS	<0.01
Li *et al*. (28)	2012	SG: n=12; NSG: n=33	Median (range): 8.2 (4.3–18.9) mo	Unilateral: n=12	Bladder	EGF	ELISA	0.031	ND	0.001	ND	NS
Taranta-Janusz *et al*. (29)	2012	SG: n=15; NSG: n=21; RG: n=19	Median (range): 0.25 (0.08–8.0) yrs	Unilateral: n=15	Bladder; pelvis	MCP1; OPN; CCL5/RANTES	ELISA	ND; NS; ND	<0.05; <0.05; No	<0.05; <0.01; No	ND	<0.05; <0.05; <0.05
Madsen *et al*. (30)	2012	SG: n=24; RG: n=13	Median (range): 8.0 (3.5–14.5) yrs	Unilateral: n=24	Bladder; pelvis	NGAL; CyC; β2M; OPN	Bead-based multiplex sandwich immunoassay	NS	ND	NS	NS	NS
Li *et al*. (31)	2012	SG: n=25; NSG: n=25; RG: n=30	Mean (standard deviation): 2.37 (±0.66) yrs	Unilateral: n=25	Bladder; pelvis	HO1	ELISA	<0.01	<0.01	<0.01	0.002	NS
Wasilewska *et al*. (32)	2011	SG: n=20; NSG: n=20; RG: n=25	Median (range): 2.16 (0.16–17) yrs	Unilateral: n=20	Bladder; pelvis	KIM1; NGAL	ELISA	ND; <0.05	<0.01; <0.01	<0.01; <0.01	NS; ND	<0.01; <0.05
Bartoli *et al*. (33)	2011	SG: n=28; NSG: n=48; RG: n=30	ND	Unilateral: n=24; bilateral: n=4	Bladder	EGF; MCP1; β2M	ELISA	ND	ND	NS; NS; 0.037	ND	ND
Kajbafzadeh *et al*. (34)	2010	SG: n=27; RG: n=27	Mean (range): 27.62 (0.5–98) yrs	Unilateral	Bladder; pelvis	CA19.9	Electrochemiluminescence enzyme immunometric kit	<0.001	ND	<0.001	ND	ND
Sager *et al*. (35)	2009	SG: n=19; RG: n=19	Mean (standard deviation): 6.7 (±5.6) yrs	Unilateral: n=18; bilateral: n=1	Bladder; pelvis	TGFβ1	ELISA	0.0001	ND	0.0001	ND	ND
Shokeir *et al*. (36)	2009	SG: n=15; NSG: n=15	ND	Unilateral: n=15	Bladder	NAG; ALP; GGT	Method of Maruhn; Synchron CX7 system; method of Bowers and McComb	ND	<0.05; <0.05; <0.001	ND	ND	ND
Taha *et al*. (37)	2007	SG: n=35; NSG: n=15	Mean (standard deviation): 5.9 (±0.71) yrs	Unilateral: n=35	Bladder	NAG; ALP; GGT	Method of Maruhn; method of Bowers and McComb; method of Szasz	3 mo post op: <0.05; 6 mo post op: <0.01; 6 mo post op: <0.01	<0.001;<0.001; <0.001	ND	ND	ND
Taha *et al*. (38)	2007	SG: n=35; RG: n=10	Mean (standard deviation): 5.9 (±0.7) yrs	Unilateral: n=35	Bladder; pelvis	ET1	ELISA	<0.05	ND	Significant	ND	ND

Table 1 (*continued*)

Table 1 (*continued*)

Reference	Year	No. of participants	Age of SG	Laterality	Urinary source	Biomarker	Method	SG pre op *vs.* SG post op	SG *vs.* NSG	SG *vs.* RG	Correlation with APD	Correlation with SRF
Taha *et al*. (39)	2007	SG: n=35; RG: n=30	Mean (range): 5.9 (0.5–12) yrs	Unilateral: n=35	Bladder	TGFβ1; EGF	ELISA	1 mo post op: <0.05; 2 mo post op: <0.05; 3 mo post op: NS; 6 mo post op: NS; 9 mo post op: NS; 12 mo post op: <0.001; 1 mo post op: NS; 2 mo post op: NS; 3 mo post op: NS; 6 mo post op: NS; 9 mo post op: NS; 12 mo post op: NS	ND; ND	<0.001;NS	ND; ND	NS; ND
Palmer *et al*. (40)	1997	SG: n=13; RG: n=19	Mean (range): 4.6 yrs (1 mo–11 yrs)	Unilateral: n=13	Bladder; pelvis	TGFβ1	ELISA	ND	ND	NS	ND	ND
El-Sherbiny *et al*. (41)	2002	SG: n=15; NSG: n=11	Mean (standard deviation): 5.2 (±4.7) yrs	Unilateral: n=15	Bladder; pelvis	TGFB1	ELISA	NS	<0.003	ND	ND	NS
Grandaliano *et al*. (42)	2000	SG: n=24; RG: n=15	Mean [range]: 24.4 [2–156] mo	Unilateral: n=24	Bladder; pelvis	MCP1 EGF	ELISA	<0.01; <0.01	ND	<0.01; <0.01	ND	<0.03; NS

Data were recorded according to the following categories: first author, year of publication, number of participants per category, age of patients undergoing pyeloplasty, PUJO laterality, source of urinary biomarkers (bladder *vs.* pelvis), type of urinary biomarker, type of laboratory test used, statistical significance between pre and postoperative biomarker concentration in patients undergoing pyeloplasty, statistical significance between biomarker concentration of patients undergoing pyeloplasty and patients with mild hydronephrosis treated conservatively, statistical significance between biomarker concentration of patients undergoing pyeloplasty and healthy children, correlation between preoperative urinary biomarker concentration and DAP, correlation between preoperative urinary biomarker concentration and SRF. PUJO, pelvic-ureteric junction obstruction (not specified of the treatment received); SG, surgical group; NSG, non-surgical group; RG, reference group; Preop, preoperatively; Intraop, intraoperatively; postop, postoperatively; DAP, anterior posterior renal pelvis diameter; SRF, split renal function; NS, not statistically significant; ND, not determined; mo, months; wks, weeks; yrs, years; IL6, interleukin 6; NGAL, neutrophil gelatinase-associated lipocalin; MCP1, monocyte chemotactic peptide-1; TGFβ1, transforming growth factor β1; CA19.9, carbohydrate antigen 19.9; KIM1, kidney injury molecule 1; α-GST, α-glutathione S-transferases; Π-GST, Π-glutathione S-transferases; DB1, B defense 1; LL37, cathelicidin; HIP/PAP, hepatocarcinoma-intestine-pancreas/pancreatitis-associated protein; HD5, human a defensin 5; TNFα, tumor necrosis factor α, Trx, thioredoxin; ICAM1, intercellular adhesion molecule 1; HEX A, exoglycosidase A, HEX B, exoglycosidase B; HEX C, exoglycosidase C; FUC, fucose; GAL, galactose; MAN, mannose; GLU, glucose; EGF, epidermal growth factor; MMP9, matrix metalloproteinase 9; TIMP1, tissue inhibitor of metalloproteinase 1; PIIINP, procollagen III aminoterminal propeptide; CCL5/RANTES, regulated on activation, normal T cell expressed and secreted; AGT, angiotensinogen; MIP1a, macrophage inflammatory protein 1a; IP10, interferon-γ-inducible protein-10; OPN, osteopontin; CyC, cystatin C; β2M, β2microglobulin; HO1, heme oxygenase 1; NAG, N-acetyl-β-D-glucosaminidase; ALP, alkaline phosphatase; GGT, γ-glutamyl transferase; ET1, endothelin 1; SEMA3A, semaphorin-3A; L-FABP, liver-type fatty acid-binding protein.

Table 2 Paediatric biomarkers of PUJO

Author	Study groups	Biomarker concentrations	Outcomes	AUC on ROC curve	BCU value	Sensibility	Specificity
NGAL (n=9; 23.7%)							
Yu *et al.* (5)	UPJO: n=17; RG: n=17	ND	UPJO *vs.* RG: 0.0004; bilateral UPJO *vs.* unilateral UPJO: <0.0001; bilateral UPJO *vs.* RG: <0.0001	0.90	ND	88%	88%
Bieniaś *et al.* (7)*	Group A: n=25; group B: n=11; group C: n=9; RG: n=21; ON: n=28; NON: n=17	Group A: 1.73 ng/mg Cr (median); group B: 1.41 ng/mg Cr; group C: 0.51 ng/mg Cr; RG: 0.83 ng/mg Cr	Group A *vs.* RG: 0.02; group B *vs.* RG: NS; group C *vs.* RG: NS; ON *vs.* NON: 0.01	ON *vs.* RG: 0.663; ON *vs.* NON: 0.805	ON *vs.* RG: 0.091 ng/mg Cr; ON *vs.* NON: 0.079 ng/mg Cr	ON *vs.* RG: 39.3%; ON *vs.* NON: 78.6%	ON *vs.* RG: 58.3%; ON *vs.* NON: 58.3%
Gupta *et al.* (8)	SG: n=30; RG: n=15	SG: 1.6 ng/mg Cr (median); RG: 4.9 ng/mg Cr	SG *vs.* RG: 0.0009	0.80	2.5999 ng/mg Cr	80%	76.7%
Gerber *et al.* (13)	SG: n=12; RG: n=12	SG: 902.68/Cr (mean); RG: 66.52/Cr	SG *vs.* RG: NS	ND	ND	ND	ND
Karakus *et al.* (15)	SG: n=13; NSG: n=19; RG: n=9	ND	SG *vs.* RG: 0.032; SG pre op *vs.* NSG: NS; SG post op 3 mo *vs.* SG pre op: <0.05; SG post op 6 mo *vs.* RG: NS	0.85 (95% CI: 0.68–1)	0.688 ng/mg Cr	84.6%	77.8%
Noyan *et al.* (17)	SG: n=26; NSG: n=36; RG: n=20	SG: 1.8 ng/mg Cr [0–16] (median); NSG: 0.9 ng/mg Cr [0–21]; RG: 0.5 ng/mg Cr [0–14]	SG *vs.* RG: <0.05; SG *vs.* NSG: <0.05	0.68 (95% CI: 0.6–0.7)	0.16 ng/mg Cr	58%	75%
Cost *et al.* (26)	SG: n=61; RG: n=22	SG bladder urine: 18.6 ng/mg (median); SG pelvic urine: 26.2 ng/mg; RG: 8.3 ng/mg	SG *vs.* RG: 0.004; SG pelvic urine *vs.* SG bladder urine: 0.004	ND	ND	ND	ND

Table 2 (*continued*)

Table 2 (*continued*)

Author	Study groups	Biomarker concentrations	Outcomes	AUC on ROC curve	BCU value	Sensibility	Specificity
Madsen *et al.* (30)	SG: n=24; RG: n=13	SG pre op: 11.9 ng/mg Cr (median); SG peri op obs: 73.3 ng/mg Cr; SG peri op non-obs: 24.0 ng/mg Cr; SG post op 1 ds obs: 130.8 ng/mg Cr; SG post op 1 ds non-obs: 27.2 ng/mg Cr; SG post op 3 wks obs: 81.9 ng/mg Cr; SG post op 3 wks bladder: 71.3 ng/mg Cr; SG post op 3 mo: 6 ng/mg Cr; SG post op 1 yrs: 10.7 ng/mg Cr; RG: 8.1 ng/mg Cr	SG peri op obs *vs.* RG: <0.05; SG peri op obs *vs.* SG peri op non-obs: <0.05; SG peri op non-obs *vs.* RG: <0.05; SG post op 1 ds obs *vs.* RG: <0.05; SG post op 1 ds obs *vs.* SG post op 1 ds non-obs: <0.05; SG post op 1 ds non-obs *vs.* RG: <0.05; SG post op 3 wks obs *vs.* RG: <0.05; SG post op 3 wks bladder *vs.* RG: <0.05; SG pre op *vs.* RG: NS; SG peri op *vs.* RG: <0.05; SG post op 1 ds *vs.* RG: <0.05; SG post op 3 wks *vs.* RG: <0.05; SG post op 3 mo *vs.* RG: NS; SG post op 1 yrs *vs.* RG: NS	0.903 (95% CI: 0.837–1)	20.57 ng/mg Cr	82%	100%
Wasilewska *et al.* (32)	SG: n=20; NSG: n=20; RG: n=25	SG pre op: 23.66 ng/mg Cr (median); SG peri op pelvis: 38.48 ng/mg Cr; SG post op 3 mo: 5.62 ng/mg Cr; NSG: 3.8 ng/mg Cr; RG: 2.31 ng/mg Cr	SG pre op *vs.* NSG: <0.05; SG pre op *vs.* RG: 0.01; SG peri op pelvis *vs.* NSG: <0.01; SG peri op pelvis *vs.* RG: <0.01; SG post op 3 mo *vs.* RG: <0.05; NSG *vs.* RG: <0.05	DRF<40% among SG and NSG: 0.814 (95% CI: 0.711–0.917); DRF<45% among all patients: 0.868 (95% CI: 0.796–0.939)	2.158 ng/mg Cr; 4.924 ng/mg Cr	100%; 82.4%	28.6%; 75.7%
MCP1 (n=8; 21.1%)							
Yu *et al.* (5)	UPJO: n=17; RG: n=17	ND	UPJO *vs.* RG: 0.0005; bilateral UPJO *vs.* unilateral UPJO: <0.001; bilateral UPJO *vs.* RG: <0.001	0.89	ND	ND	ND
Sadeghi-Bojd *et al.* (10)	SG: n=20; NSG: n=20; RG: n=30	SG: 58.94 ng/L Cr (mean); NSG: 39.58 ng/L Cr; RG: 33.10 ng/L Cr	SG *vs.* NSG: 0.005; SG *vs.* RG: 0.001	ND	ND	ND	ND
Karakus *et al.* (15)	SG: n=13; NSG: n=19; RG: n=9	ND	SG pre op *vs.* RG: 0.002; SG pre op *vs.* NSG: 0.037; SG post op 3 mo *vs.* RG: NS	0.93 (95% CI: 0.83–1)	272.3 pg/mg Cr	84.6%	88.9%
Mohammadjafari *et al.* (20)	SG: n=24; NSG: n=24	SG: 1.47 ng/mg Cr (0.86–2.36); NSG: 0.46 ng/mg Cr (0.33–0.81)	SG *vs.* NSG: 0.012	0.723 (95% CI: 0.568–0.896)	0.9270 ng/mg Cr	77%	72%
Madsen *et al.* (24)	SG: n=28; RG: n=13	SG pre op: 136.9 pg/mg Cr (median); SG peri op obs: 195.3 pg/mg Cr; SG peri op non-obs: 190.6 pg/mg Cr; SG post op 1 ds obs: 677.7 pg/mg Cr; SG post op 1 ds non-obs: 110.8 pg/mg Cr; SG post op 3 wks obs: 172.2 pg/mg Cr; SG post op 3 wks bladder: 140.2 pg/mg Cr; SG post op 3 mo: 95.8 pg/mg Cr; SG post op 1 yr: 80.8 pg/mg Cr; RG: 80.1 pg/mg Cr	SG pre op *vs.* RG: 0.005; SG peri op obs *vs.* RG: <0.05; SG peri op obs *vs.* SG peri op non-obs: <0.05; SG peri op non-obs *vs.* RG: <0.05; SG post op 1 ds obst *vs.* RG: <0.05; SG post op 1 ds obs *vs.* SG post op 1 ds non-obs: <0.05; SG post op 3 wks obs *vs.* RG: <0.05; SG post op 3 wks obs *vs.* SG post op 3 wks bladder: <0.05; SG post op 3 mo *vs.* RG: NS; SG post op 1 yr *vs.* RG: NS; SG pre op *vs.* SG post op 1 yr: NS	0.78 (95% CI: 0.63–0.92)	93.199 pg/mg Cr	77.8%	69.3%
Taranta-Janusz *et al.* (29)	SG: n=15; NSG: n=21; RG: n=19	SG pre op: 76.77 pg/mL pg/mg Cr (median); SG pelvis: 94.07 pg/mL pg/mg Cr; SG 3 mo post op: 56.1 pg/ml pg/mg Cr; NSG: 14.04 pg/mL pg/mg Cr; RG: 9.17 pg/mL pg/mg Cr	SG pre op *vs.* NSG: <0.05; SG pre op *vs.* RG: <0.05; SG pelvis *vs.* NSG: <0.01; SG pelvis *vs.* RG: <0.01; SG 3 mo post op *vs.* NSG: <0.05; SG 3 mo post op *vs.* RG: <0.01	0.704 (95% CI: 0.581–0.827)	0.45 pg/mg Cr	100%	0%
Bartoli *et al.* (33)[#]	O-UPJO: n=12; F-UPJO: n=36; OPER: n=28; RG: n=30	ND	OPER *vs.* O-UPJO: <0.05; OPER *vs.* F-UPJO: <0.05; O-UPJO *vs.* RG: <0.001; F-UPJO *vs.* RG: <0.01	ND	ND	ND	ND
Grandaliano *et al.* (42)	SG: n=24; RG: n=15	ND	SG pre op *vs.* RG: <0.01; SG pre op *vs.* SG post op: <0.01	ND	ND	ND	ND
TGFβ1 (n=7; 18.4%)							
Yu *et al.* (5)	UPJO: n=17; RG: n=17	ND	UPJO *vs.* RG: NS; Bilateral UPJO *vs.* Unilateral UPJO: NS; Bilateral UPJO *vs.* RG: NS	0.56	ND	ND	ND
Merrikhi *et al.* (23)	SG: n=25; RG: n=25	SG: 87.1 pg/mL (mean) RG: 14.5 pg/mL	SG *vs.* RG: 0.001	ND	ND	ND	ND

Table 2 (*continued*)

Table 2 (*continued*)

Author	Study groups	Biomarker concentrations	Outcomes	AUC on ROC curve	BCU value	Sensibility	Specificity
Gawłowska-Marciniak *et al.* (25)	SG: n=45 (young children: n=7; older children: n=20; adolescents: n=18); RG: n=25 (young children: n=5; older children: n=5; adolescents: n=15)	SG pelvic urine young children 4,495.18 pg/mg Cr (mean); SG pelvic urine older children 3,869.00 pg/mg Cr; SG pelvic urine adolescents 1,283.54 pg/mg Cr; SG bladder urine young children 4,652.33 pg/mg Cr (mean); SG bladder urine older children 1,727.09 pg/mg Cr; SG bladder urine adolescents 854.44 pg/mg Cr; RG bladder urine young children 4,111.71 pg/mg Cr (mean); RG bladder urine older children 1,370.29 pg/mg Cr; RG bladder urine adolescents 481.50 pg/mg Cr; SG bladder urine young children 12 mo post op 595.44 pg/mg Cr (mean); SG bladder urine older children 12 mo post op 602.84 pg/mg Cr; SG bladder urine adolescents children 12 mo post op 450.96 pg/mg Cr	SG pelvic urine older children *vs.* RG bladder urine older children: <0.05; SG pelvic urine adolescents *vs.* RG bladder urine adolescents: <0.05; SG pelvic urine young children *vs.* SG pelvic urine adolescent: <0.001; SG bladder urine young children *vs.* SG bladder urine adolescent: <0.001; SG bladder urine young children *vs.* SG bladder urine older children: <0.001; SG bladder urine young children pre op *vs.* SG bladder urine young children 12 mo post op: <0.05; SG bladder urine older children pre op *vs.* SG bladder urine older children 12 mo post op: <0.05	ND	ND	ND	ND
Sager *et al.* (35)	SG: n=19; RG: n=19	SG pre op: 92.5 pg/mL (mean); RG: 35.8 pg/mL; SG peri op pelvis: 122.3 pg/mL; SG post op: 48.7 pg/mL	SG pre op *vs.* RG: 0.0001; SG peri op pelvis *vs.* SG pre op: <0.05; SG post op *vs.* SG pre op: 0.0001	ND	ND	ND	ND
Taha *et al.* (39)	SG: n=35; RG: n=30	SG pre op: 374 pg/mg Cr; SG post op 1 yr: 157 pg/mg Cr; SG pre op < 1 yr: 601 pg/mg Cr; SG pre op > 1 yr: 307 pg/mg Cr; RG: 157 pg/mg Cr	SG pre op *vs.* RG: <0.001; SG post op 1 mo *vs.* SG pre op: <0.05; SG post op 1 mo *vs.* RG: <0.001; SG post op 2 mo *vs.* SG pre op: <0.05; SG post op 2 mo *vs.* RG: <0.001; SG post op 3 mo *vs.* SG pre op: NS; SG post op 3 mo *vs.* RG: <0.001; SG post op 6 mo *vs.* SG pre op: NS; SG post op 6 mo *vs.* RG: <0.001; SG post op 9 mo *vs.* SG pre op: NS; SG post op 9 mo *vs.* RG: <0.001; SG post op 12 mo *vs.* SG pre op: <0.001; SG post op 12 mo *vs.* RG: NS; SG pre op <1 yr *vs.* SG pre op >1 yr: <0.01	ND	190 pg/mg Cr; <1 yr: 330 pg/mg Cr; >1 yr: 200 pg/mg Cr	100%; 100%; 100%	80%; 100%; 76.7%
Palmer *et al.* (40)	SG: n=13; RG: n=19	SG bladder: 31.2 pg/mL (mean); SG pelvis: 82.4 pg/mL; RG: 26.6 pg/mL	SG pelvis *vs.* SG urine: 0.03; SG bladder *vs.* RG: NS	ND	ND	ND	ND
El-Sherbiny *et al.* (41)	SG: n=15; NSG: n=11	SG bladder pre op: 68 pg/mg Cr (mean); SG pelvis per op: 285 pg/mg Cr; SG bladder post op 3 mo: 39 pg/mg Cr; NSG bladder: 22 pg/mg Cr; SG pelvis peri op < 1 yrs: 465 pg/mg Cr; SG pelvis peri op > 1 yrs: 218 pg/mg Cr	SG pre op *vs.* NSG: <0.003; SG post op 3 mo *vs.* SG pre op: NS; SG bladder <1 yr *vs.* SG bladder > 1 yr: NS; NSG bladder < 1 yr *vs.* NSG bladder > 1 yr: NS; SG pelvis peri op <1 yr *vs.* SG pelvis peri op >1 yr: <0.04	ND	29 pg/mg Cr	80%	82%
EGF (n=6; 15.8%)							
Mohammadjafari *et al.* (21)	SG: n=24; NSG: n=18; RG: n=17	SG: 21.07 ng/mg Cr (median); NSG: 12.86 ng/mg Cr; RG: ND	SG *vs.* NSG: 0.016	0.728 (95% CI: 0.560–0.896)	16.855 ng/mg Cr	71%	77%
Madsen *et al.* (24)	SG: n=28; RG: n=13	SG pre op: 7.4 ng/mg Cr (median); SG peri op obs: 10.4 ng/mg Cr; SG peri op non-obs: 10.9 ng/mg Cr; SG post op 1 ds obs: 12.9 ng/mg Cr; SG post op 1 ds non-obs: 5.6 ng/mg Cr; SG post op 3 wks obs: 9.5 ng/mg Cr; SG post op 3 wks bladder: 7.2 ng/mg Cr; SG post op 3 mo: 4.6 ng/mg Cr; SG post op 1 yr: 3.5 ng/mg Cr; RG: 4.0 ng/mg Cr	SG pre op *vs.* RG: 0.012; SG peri op obs *vs.* RG: <0.05; SG peri op non-obs *vs.* RG: <0.05; SG post op 1 ds obs *vs.* RG: <0.05; SG post op 1 ds obs *vs.* SG post op 1 ds non-obs: <0.05; SG post op 3 wks obs *vs.* RG: <0.05; SG post op 3 wks obs *vs.* SG post op 3 wks bladder: <0.05; SG post op 3 mo *vs.* RG: NS; SG post op 1 yr *vs.* RG: NS; SG pre op *vs.* SG post op 1 yr: NS	0.75 (95% CI: 0.60–0.90)	4.71 ng/mg Cr	70.4%	69.2%
Li *et al.* (28)	SG: n=12; NSG: n=33	SG <6 mo post birth: 38 ng/mg Cr (median); SG pre op: 46; SG 3–12 mo post op: 55 ng/mg Cr; NSG <6 mo post birth: 50 ng/mg Cr; NSG 6–12 mo post birth: 59 ng/mg Cr; NSG >12 mo post birth: 69.5 ng/mg Cr	NSG <6 mo post birth *vs.* NSG 6–12 mo post birth: 0.015; NSG <6 mo post birth *vs.* NSG >12 mo post birth: <0.01; NSG 6–12 mo post birth *vs.* NSG >12 mo post birth: 0.017; SG <6 mo post birth *vs.* SG 3–12 mo post op: <0.01; SG <6 mo post birth *vs.* SG pre op: NS; NSG <6 mo post birth *vs.* SG <6 mo post birth: 0.001	0.789	42 ng/mg Cr	84.8%	75%
Bartoli *et al.* (33)[#]	O-UPJO: n=12; F-UPJO: n=36; OPER: n=28; RG: n=30	ND	O-UPJO *vs.* RG: <0.05; O-UPJO *vs.* F-UPJO: <0.05	ND	ND	ND	ND

Table 2 (*continued*)

Table 2 (*continued*)

Author	Study groups	Biomarker concentrations	Outcomes	AUC on ROC curve	BCU value	Sensibility	Specificity
Taha *et al.* (39)	SG: n=35; RG: n=30	SG pre op: 54.5 pg/mg Cr; SG pre op <1 yr: 91.0 pg/mg Cr; SG pre op >1 yr: 43.7 pg/mg Cr; RG: 54.3 pg/mg Cr	SG pre op *vs.* RG: NS; SG post op 1 mo *vs.* SG pre op: NS; SG post op 1 mo *vs.* RG: NS; SG post op 2 mo *vs.* SG pre op: NS; SG post op 2 mo *vs.* RG: NS; SG post op 3 mo *vs.* SG pre op: NS; SG post op 3 mo *vs.* RG: NS; SG post op 6 mo *vs.* SG pre op: NS; SG post op 6 mo *vs.* RG: NS; SG post op 9 mo *vs.* SG pre op: NS; SG post op 9 mo *vs.* RG: NS; SG post op 12 mo *vs.* SG pre op: NS; SG post op 12 mo *vs.* RG: NS; SG pre op <1 yr *vs.* SG pre op >1 yr: significant	ND	40 pg/mg Cr; <1 yr: ND; >1 yr: 50 pg/mg Cr	40%; ND; 81.5%	80%; ND; 53.3%
Grandaliano *et al.* (42)	SG: n= 24; RG: n=15	ND	SG pre op *vs.* RG: <0.01; SG pre op *vs.* SG post op: <0.01	ND	ND	ND	ND
KIM1 (n=6; 15.8%)							
Bieniaś *et al.* (7)*	Group A: n=25; Group B: n=11; group C: n=9; RG: n=21; ON: n=28; NON: n=17	Group A: 2.4 ng/mg Cr (median); group B: 0.58 ng/mg Cr; group C: 0.68 ng/mg Cr; RG: 0.28 ng/mg Cr	Group A *vs.* control group: 0.02; group B *vs.* control group: 0.02; group C *vs.* control group: NS; ON *vs.* NON: NS	ON *vs.* RG: 0.653; ON *vs.* NON: 0.487	ON *vs.* RG: 0.084 ng/mg Cr; ON *vs.* NON: 0.119 ng/mg Cr	ON *vs.* RG: 55.6%; ON *vs.* NON: 88.9%	ON *vs.* RG: 69.6%; ON *vs.* NON: 16.7%
Gerber *et al.* (13)	SG: n=12; RG: n=12	SG: 4.67/Cr (mean); RG: 5.58/Cr	SG *vs.* RG: NS	ND	ND	ND	ND
Karakus *et al.* (15)	SG: n=13; NSG: n=19; RG: n=9	ND	SG pre op *vs.* RG: 0.001; SG pre op *vs.* NSG: NS; SG post op 3 mo *vs.* RG: NS	0.89 (95% CI: 0.72–1)	0.687 ng/mg Cr	92.3%	83.3%
Noyan *et al.* (17)	SG: n=26; NSG: n=36; RG: n=20	SG: 169 ng/mg Cr [39–2,809] (median); NSG: 215 ng/mg Cr [37–1,351]; RG: 159 ng/mg Cr [6–525]	SG *vs.* NSG: NS; SG *vs.* RG: NS	ND	ND	ND	ND
Mohammadjafari *et al.* (21)	SG: n=24 NSG: n=18 RG: n=17	SG: 0.97 ng/mg Cr (median); NSG: 0.40 ng/mg Cr; RG: ND	SG *vs.* NSG: 0.015	0.731 (95% CI: 0.557–0.905)	0.4765 ng/mg Cr	81%	71%
Wasilewska *et al.* (32)	SG: n=20 NSG: n=20 RG: n=25	SG pre op: 3.13 ng/mg Cr (median); SG peri op pelvis: 3.42 ng/mg Cr; SG post op 3 mo: 1.73 ng/mg Cr; NSG: 1.04 ng/mg Cr; RG: 0.58 ng/mg Cr	SG pre op *vs.* NSG: <0.05; SG pre op *vs.* RG: 0.01; SG peri op pelvis *vs.* NSG: <0.01; SG peri op pelvsi *vs.* RG: <0.01; SG post op 3 mo *vs.* NSG: <0.05; SG post op 3 mo *vs.* RG: <0.01	0.8 (95% CI: 0.687–0.914)	0.462 ng/mg Cr	100%	71.4%
CCL5/RANTES (n=3; 7.9%)							
Madsen *et al.* (24)	SG: n=28; RG: n=13	SG pre op: 0 pg/mg Cr (median); SG peri op obs: 89.2 pg/mg Cr; SG peri op non-obs: 0 pg/mg Cr; SG post op 1 ds obs: 475.6 pg/mg Cr; SG post op 1 ds non-obs: 55.6 pg/mg Cr; SG post op 3 wks obs: 34.3 pg/mg Cr; SG post op 3 wks bladder: 29.9 pg/mg Cr; SG post op 3 mo: 0 pg/mg Cr; SG post op 1 yr: 0 pg/mg Cr RG: 0 pg/mg Cr	SG pre op *vs.* RG: NS; SG peri op obs *vs.* RG: <0.05; SG peri op obs *vs.* SG peri op non-obs: <0.05; SG peri op non-obs *vs.* RG: <0.05; SG post op 1 ds *vs.* RG: <0.05; SG post op 1 ds obs *vs.* SG post op 1 ds non-obs: <0.05; SG post op 1 ds non-obs *vs.* RG: <0.05; SG post op 3 wks obs *vs.* RG: <0.05; SG post op 3 wks bladder *vs.* RG: <0.05; SG post op 3 mo *vs.* RG: NS; SG post op 1 yr *vs.* RG: NS	ND	ND	ND	ND
Gawłowska-Marciniak *et al.* (25)	SG: n=45 (young children: n=7; older children: n=20; adolescents: n=18); RG: n=25 (young children: n=5; older children: n=5; adolescents: n=15)	SG pelvic urine young children: 780.12 pg/mg Cr (mean); SG pelvic urine older children: 312.23 pg/mg Cr; SG pelvic urine adolescents: 150.63 pg/mg Cr; SG bladder urine young children: 768.33 pg/mg Cr (mean); SG bladder urine older children: 188.40 pg/mg Cr; SG bladder urine adolescents: 135.19 pg/mg Cr; RG bladder urine young children: 351.86 pg/mg Cr; RG bladder urine older children: 204.03 pg/mg Cr; RG bladder urine adolescents: 91.51 pg/mg Cr; SG bladder urine young children 12 mo post op: 50.68 pg/mg Cr; SG bladder urine older children 12 mo post op 91.96 pg/mg Cr; SG bladder urine adolescents children 12 mo post op 39.57 pg/mg Cr	SG pelvic urine young children *vs.* RG bladder urine young children: <0.05; SG pelvic urine older children *vs.* RG bladder urine older children: <0.05; SG pelvic urine young children *vs.* SG pelvic urine older children: <0.05; SG bladder urine young children *vs.* SG bladder urine older children: <0.05 SG pelvic urine young children *vs.* SG pelvic urine adolescents: <0.01; SG bladder urine young children *vs.* SG bladder urine adolescents: <0.01; SG bladder urine young children *vs.* SG bladder urine young children 12 mo post op: <0.05; SG bladder urine adolescents *vs.* SG bladder urine adolescents 12 mo post op: <0.05	ND	ND	ND	ND

Table 2 (*continued*)

Table 2 (*continued*)

Author	Study groups	Biomarker concentrations	Outcomes	AUC on ROC curve	BCU value	Sensibility	Specificity
Taranta-Janusz *et al.* (29)	SG: n=15; NSG: n=21; RG: n=19	SG pre op: 21.29 pg/mL pg/mg Cr (median); SG pelvis: 45.42 pg/mL pg/mg Cr; SG 3 mo post op: 31.11 pg/mL pg/mg Cr; NSG: 35.33 pg/mL pg/mg Cr; RG: 13.2 pg/mL pg/mg Cr	SG pelvis *vs.* NSG: <0.01; SG pelvis *vs.* RG: <0.01; SG 3 mo post op *vs.* NSG: <0.05; SG 3 mo post op *vs.* RG: <0.01	0.693 (95% CI: 0.58–0.807)	0.865 pg/mg Cr	100%	0%
CA19.9 (n=3; 7.9%)							
Nabavizadeh *et al.* (6)°	SG delayed: SG: n=24; SG early: n=34; NSG: n=54	NSG: 37.83 U/mL (mean); SG delayed: 145.45 U/mL; SG early: 244.62 U/mL	NSG *vs.* SG delayed *vs.* SG early: <0.001; NSG *vs.* SG delayed: <0.07	0.87 (95% CI 0.79–0.94)	52.6 U/mL	92.0%	70.9%
Atar *et al.* (18)	SG: n=17; NSG: n=17; RG: n=21	SG: 143 U/mL (mean); NSG: 67.8 U/mL; RG: 13.2 U/mL; SG 3 mo post op: 55 U/mL	SG *vs.* NSG: 0.007; SG *vs.* RG: 0.001; NSG *vs.* RG: NS; SG *vs.* SG 3 mo post op: 0.039	SG *vs.* NSG: 0.8 (95% CI: 0.634–0.981); Obs *vs.* non-obs: 0.8	15.7 U/mL; 85.5 U/mL	100%; 76%	21%; 85%
Kajbafzadeh *et al.* (34)	SG: n=27; RG: n=27	SG pre op: 319.20 U/mL (mean); SG post op 3 mo: 53.82 U/mL; SG post op 9 mo: 18.40 U/mL; SG peri op pelvis: 1,765.67 U/mL; RG: 16.91 U/mL	SG pre op *vs.* RG: <0.001; SG post op 3 mo op *vs.* RG: <0.001; SG post op 3 mo *vs.* SG pre op: <0.001; SG post op 9 mo *vs.* SG pre op: <0.001; SG peri op pelvis *vs.* SG pre op: <0.001	ND	30.6 U/mL	100%	82.6%
NAG (n=3; 7.9%)							
Mohammadjafari *et al.* (20)	SG: n=24; NSG: n=24	SG: 1.36 IU/mg Cr (0.77–2.74); NSG: 0.89 IU/mg Cr (0.49–1.71)	SG *vs.* NSG: NS	0.627 (95% CI: 0.5–0.844)	1.1913 IU/mg Cr	62%	67%
Shokeir *et al.* (36)	SG: n=15; NSG: n=15	SG: 8.34 mU/mg Cr (mean); NSG: 6.91 mU/mg Cr	SG *vs.* NSG: <0.05	ND	ND	ND	ND
Taha *et al.* (37)	SG: n=35; NSG: n=15	SG pre op: 12.68 mU/mg Cr (mean); SG post op 1 mo: 14.08 mU/mg Cr; SG post op 2 mo: 11.75 mU/mg Cr; SG post op 3 mo: 9.96 mU/mg Cr; SG post op 6 mo: 9.38 mU/mg Cr; SG post op 9 mo: 6.97 mU/mg Cr; SG post op 12 mo: 5.12 mU/mg Cr; NSG: 6.52 mU/mg Cr mU/mg Cr; SG pre op <1 yr: 19.37; mU/mg Cr mU/mg Cr; SG pre op >1 yr: 10.69 mU/mg Cr mU/mg Cr	SG *vs.* NSG: <0.001; SG post op 3 mo *vs.* SG pre op: <0.05; SG pre op <1 yr *vs.* SG pre op >1 yr: significant	ND	7.8 mU/mg Cr	97.1%	80%
ALP (n=2; 5.3%)							
Shokeir *et al.* (36)	SG: n=15; NSG: n=15	SG: 40.35 UI/g Cr (mean) NSG: 28.74 UI/g Cr	SG *vs.* NSG: <0.05	ND	ND	ND	ND
Taha *et al.* (37)	SG: n=35; NSG: n=15	SG pre op: 63.97 IU/gm Cr (mean); SG post op 1 mo: 67.61 IU/gm Cr; SG post op 2 mo: 55.01 IU/gm Cr; SG post op 3 mo: 51.76 IU/gm Cr; SG post op 6 mo: 39.65 IU/gm Cr; SG post op 9 mo: 41.8 IU/gm Cr; SG post op 12 mo: 17.72 IU/gm Cr; NSG: 27.34 IU/gm Cr; SG pre op <1 yr: 114.66 IU/gm Cr; SG pre op >1 yr: 48.95 IU/gm Cr	SG pre op *vs.* NSG: <0.001; SG post op 6 mo *vs.* SG pre op: <0.01; SG pre op <1 yr *vs.* SG pre op >1 yr: significant	ND	34.5 IU/gm Cr	91.4%	100%
GGT (n=2; 5.3%)							
Shokeir *et al.* (36)	SG: n=15; NSG: n=15	SG: 49.54 UI/g Cr (mean); NSG: 57.21 UI/g Cr	SG *vs.* NSG: <0.001	ND	ND	ND	ND
Taha *et al.* (37)	SG: n=35; NSG: n=15	SG pre op: 103.09 IU/gm Cr (mean); SG post op 1 mo: 115.16 IU/gm Cr; SG post op 2 mo: 110.68 IU/gm Cr; SG post op 3 mo: 117.69 IU/gm Cr; SG post op 6 mo: 70.25 IU/gm Cr; SG post op 9 mo: 73.69 IU/gm Cr; SG post op 12 mo: 42.39 IU/gm Cr; NSG: 46.50 IU/mg Cr; SG pre op <1 yr: 206.65 IU/gm Cr mU/g Cr; SG pre op >1 yr: 72.41 IU/gm Cr mU/g Cr	SG pre op *vs.* NSG: <0.001; SG post op 6 mo *vs.* SG pre op: <0.01; SG pre op <1 yr *vs.* SG pre op >1 yr: significant	ND	54 IU/gm Cr	62.9%	100%
IP10 (n=2; 5.3%)							
Karakus *et al.* (15)	SG: n=13; NSG: n=14; RG: n=9	ND	SG pre op *vs.* NSG: 0.038; SG pre op *vs.* RG: 0.024; SG pre op *vs.* SG post op 3 yrs: NS	0.68 (95% CI: 0.44–0.92)	298.8 pg/mg Cr	61.5%	88.9%

Table 2 (*continued*)

Table 2 (*continued*)

Author	Study groups	Biomarker concentrations	Outcomes	AUC on ROC curve	BCU value	Sensibility	Specificity
Madsen *et al.* (24)	SG: n=28; RG: n=13	SG pre op: 150 pg/mg Cr (median); SG peri op obs: 362.4 pg/mg Cr; SG peri op non-obs: 317.1 pg/mg Cr; SG post op 1 ds obs: 699.0 pg/mg Cr; SG post op 1 ds non-obs: 213 pg/mg Cr; SG post op 3 wks obs: 314.5 pg/mg Cr; SG post op 3 wks non-obs: 237.1 pg/mg Cr; SG post op 3 mo: 83.5 pg/mg Cr; SG post op 1 ys: 59.7 pg/mg Cr; RG: 68.2 pg/mg Cr	SG pre op *vs.* RG: NS; SG peri op *vs.* RG: <0.05; SG peri op obs *vs.* SG peri op non-obs: <0.05; SG peri op non-obs *vs.* RG: <0.05; SG post op 1 ds *vs.* RG: <0.05; SG post op 1 ds obs *vs.* SG post op 1 ds non-obs: <0.05; SG post op 1 ds non-obs *vs.* RG: <0.05; SG post op 3 wks *vs.* RG: <0.05; SG post op 3 wks bladder *vs.* RG: <0.05; SG post op 3 mo *vs.* RG: NS; SG post op 1 ys *vs.* RG: NS	ND	ND	ND	ND
ET1 (n=2; 5.3%)							
Mohammadjafari *et al.* (20)	SG: n=24; NSG: n=24	SG pre op: 0.88 ng/mg Cr (0.55–1.23); NSG pre op: 0.46 ng/mg Cr (0.33–0.81)	SG pre op *vs.* NSG pre op: NS	0.657 (95% CI: 0.473–0.841)	0.7509 ng/mg Cr	75%	67%
Taha *et al.* (38)	SG: n=35; RG: n=10	SG pre op: 6.56 fmol/mg Cr (mean); SG peri op pelvis: 18.18 fmol/mg Cr; SG post op 1 mo: 11.95 fmol/mg Cr; SG post op 2 mo: 9.99 fmol/mg Cr; SG post op 3 mo: 8.24 fmol/mg Cr; SG post op 6 mo: 7.72 fmol/mg Cr; SG post op 9 mo: 6.49 fmol/mg Cr; SG post op 12 mo: 4.44 fmol/mg Cr; RG: 1.7 fmol/mg Cr; SG <1 yr: 12.37 fmol/mg Cr; SG >1 yr: 4.84 fmol/mg Cr	SG peri op pelvis *vs.* SG pre op: <0.001; SG post op 1 mo *vs.* SG post op 1 mo: <0.001; SG post op 2 mo *vs.* SG post op 2 mo: <0.001; SG post op 3 mo *vs.* SG post op 3 mo: <0.05; SG post op 6 mo *vs.* SG post op 6 mo: NS; SG post op 9 mo *vs.* SG post op 9 mo: NS; SG post op 12 mo *vs.* SG post op 12 mo: <0.05; SG pre op *vs.* RG: significant; SG <1 yr *vs.* SG >1 yr: <0.001	ND	3 fmol/mg Cr; 4 fmol/mg Cr (SG <1 yr); 2.5 fmol/mg Cr (SG >1 yr)	74.3%; 100%; 81.5%	90%; 100%; 76.7%
β2M (n=2; 5.3%)							
Madsen *et al.* (30)	SG: n=24; RG: n=13	SG pre op: 109.8 ng/mg Cr (median); SG peri op obs: 207.5 ng/mg Cr; SG peri op non-obs: 172.5 ng/mg Cr; SG post op 1 ds obs: 267.6 ng/mg Cr; SG post op 1 ds non-obs: 81.8 ng/mg Cr; SG post op 3 wks obs: 152.4 ng/mg Cr; SG post op 3 wks bladder: 131.7 ng/mg Cr; SG post op 3 mo: 100.2 ng/mg Cr; SG post op 1 yr: 99.5 ng/mg Cr; RG: 113.6 ng/mg Cr	SG peri op obs *vs.* RG: <0.05; SG peri op non-obs *vs.* RG: <0.05; SG post op 1 ds obs *vs.* RG: <0.05; SG post op 1 ds obs *vs.* SG post op 1 ds non-obs: <0.05; SG post op 3 wks *vs.* RG: <0.05; SG peri op *vs.* RG: <0.05; SG post op 1 ds *vs.* RG: <0.05	0.811 (95% CI: 0.661–0.952)	191.8 ng/mg Cr	68%	92%
Bartoli *et al.* (33)[#]	O-UPJO: n=12; F-UPJO: n=36; OPER: n=28; RG: n=30	ND	OPER *vs.* RG: <0.05; OPER *vs.* F-UPJO: <0.01; OPER *vs.* 0-UPJO: <0.01; O-UPJO *vs.* RG: <0.01; F-UPJO *vs.* RG: <0.05	ND	ND	ND	ND
CyC (n=2; 5.3%)							
Karakus *et al.* (15)	SG: n=13; NSG: n=19; RG: n=9	ND	SG *vs.* RG: NS; SG *vs.* NSG: NS; NSG *vs.* RG: 0.004; SG pre op *vs.* SG post op: NS	ND	ND	ND	ND
Madsen *et al.* (30)	SG: n=24; RG: n=13	SG pre op: 99.0 ng/mg Cr (median); SG peri op obs: 122.3 ng/mg Cr; SG peri op non-obs: 116.2 ng/mg Cr; SG post op 1 ds obs: 151.2 ng/mg Cr; SG post op 1 ds non-obs: 67.9 ng/mg Cr; SG post op 3 wks obs: 111.5 ng/mg Cr; SG post op 3 wks bladder: 110.2 ng/mg Cr; SG post op 3 mo: 85.2 ng/mg Cr; SG post op 1 yr: 74.2 ng/mg Cr; RG: 99.5 ng/mg Cr	SG peri op obs *vs.* RG: <0.05; SG post op 1 ds obs *vs.* RG: <0.05; SG post op 1 ds obs *vs.* SG post op 1 ds non-obs: <0.05	ND	ND	ND	ND
OPN (n=2; 5.3%)							
Taranta-Janusz *et al.* (29)	SG: n=15; NSG: n=21; RG: n=19	SG pre op: 52.29 ng/mL ng/mg Cr (median); SG pelvis: 73.1 ng/mL ng/mg Cr; SG 3 mo post op: 80.52 ng/mL ng/mg Cr; NSG: 19.37 ng/mL ng/mg Cr; RG: 39.32 ng/mL ng/mg Cr	SG pelvis *vs.* NSG: <0.01; SG pelvis *vs.* RG: <0.01; SG 3 mo post op *vs.* NSG: <0.01; SG 3 mo post op *vs.* RG: <0.01	0.666 (95% CI: 0.544–0.787)	5.502 ng/mg Cr	98.5%	10.5%
Madsen *et al.* (30)	SG: n=24; RG: n=13	SG pre op: 1,664.9 ng/mg Cr (median); SG peri op obs: 1,218.9 ng/mg Cr; SG peri op non-obs: 1,439.3 ng/mg Cr; SG post op 1 ds obs: 2,131.7 ng/mg Cr; SG post op 1 ds non-obs: 769.0 ng/mg Cr; SG post op 3 wks obs: 1,282.0 ng/mg Cr; SG post op 3 wks bladder: 1,168.8 ng/mg Cr; SG post op 3 mo: 1,295.9 ng/mg Cr; SG post op 1 yr: 1,409.4 ng/mg Cr; RG: 1,139.7 ng/mg Cr	SG post op 1 ds obs *vs.* RG: <0.05; SG post op 1 ds obs *vs.* SG post op 1 ds non-obs: <0.05	ND	ND	ND	ND

Table 2 (*continued*)

Table 2 (*continued*)

Author	Study groups	Biomarker concentrations	Outcomes	AUC on ROC curve	BCU value	Sensibility	Specificity
ICAM1 (n=1; 2.6%)							
Taranta-Janusz *et al.* (14)	SG: n=29; NSG: n=23; RG: n=19	SG pre op: 44.36 ng/mg Cr (median); SG post op: 34.23 ng/mg Cr; NSG: 14.98 ng/mg Cr; RG: ND	SG pre op *vs.* SG post op: NS; SG pre op *vs.* NSG: <0.05; SG post op *vs.* NSG: <0.05; SG pre op *vs.* RG: <0.01	0.845 (95% CI: 0.728–0.962)	9.486 ng/mg Cr	87.8%	70.6%
HO 1 (n=1; 2.6%)							
Li *et al.* (31)	SG: n=25; NSG: n=25; RG: n=30	SG pre op: 4.23 ng/mg Cr (mean); SG peri op pelvis: 4.43 ng/mg Cr; SG post op 1 mo: 1.73 ng/mg Cr; NSG: 1.04 ng/mg Cr; RG: 0.56 ng/mg Cr	SG pre op *vs.* NSG: <0.01; SG pre op *vs.* RG: <0.01; SG peri op pelvis *vs.* NSG: <0.01; SG peri op pelvis *vs.* RG: <0.01; SG post op 3 mo *vs.* NSG: <0.05; SG post op 3 mo *vs.* RG: <0.01; NSG *vs.* RG: <0.05	0.767 (95% CI: 0.624–0.910)	1.92 ng/mg Cr	72.2	78.1
AGT (n=1; 2.6%)							
Taranta-Janusz *et al.* (27)	SG: n=31; NSG: n=20; RG: n=19	SG: 0.37 ng/mg Cr (median); NSG: 0.17 ng/mg Cr; RG: 0.16 ng/mg Cr	SG *vs.* NSG: <0.01; SG pre op *vs.* NSG: <0.05; SG post op *vs.* NSG: <0.05; SG *vs.* RG: <0.01; NSG *vs.* RG: NS	0.838 (95% CI: 0.725–0.951)	0.195 ng/mg Cr	93.3%	60.0%
Emmprin (n=1; 2.6%)							
Tian *et al.* (19)	SG: n=15; NSG: n=25	SG: 49.3 ng/mg Cr (median); NSG: 33.7 ng/mg Cr	SG *vs.* NSG: <0.0001	0.877	33.1 ng/mg Cr	76%	83%
MMP9 (n=1; 2.6%)							
Tian *et al.* (19)	SG: n=15; NSG: n=25	SG: 33.9 ng/mg Cr (median); NSG: 28.2 ng/mg Cr	SG *vs.* NSG: <0.05	0.727	27.15 ng/mg Cr	88%	67%
TIMP1 (n=1; 2.6%)							
Tian *et al.* (19)	SG: n=15; NSG: n=25	SG: 7.4 ng/mg Cr (median); NSG: 5.6 ng/mg Cr	NS *vs.* NSG: <0.05	0.823	5.35 ng/mg Cr	80%	83%
MIP1a (n=1; 2.6%)							
Madsen *et al.* (24)	SG: n=28; RG: n=13	SG pre op: 0 pg/mg Cr (median); SG peri op obs: 32.3 pg/mg Cr; SG peri op non-obs: 0 pg/mg Cr; SG post op 1 ds obs: 32.8 pg/mg Cr; SG post op 1 ds non-obs: 10.2 pg/mg Cr; SG post op 3 wks obs: 0 pg/mg Cr; SG post op 3 wks non-obs: 0 pg/mg Cr; SG post op 3 mo: 0 pg/mg Cr; SG post op 1 yr: 0 pg/mg Cr; RG: 4.7 pg/mg Cr	SG pre op *vs.* RG: <0.05; SG peri op obs *vs.* SG peri op non-obs: <0.05; SG post op 1 ds obs *vs.* RG: <0.05; SG post op 3 mo *vs.* RG: <0.05	ND	ND	ND	ND
PIIINP (n=1; 2.6%)							
Jianguo *et al.* (22)	SG: n=29; NSG: n=30; RG: n=30	SG pre op: 592.3 pg/mL Cr (median); SG 3 ds post op: 699 pg/mL Cr; SG 3 mo post op: 307.8 pg/mL Cr; SG 6 mo post op: 305.1 pg/mL Cr; SG 1 yr post op: 322.8 pg/mL Cr; NSG: 264 pg/mL Cr; RG: 237pg/mL Cr	SG pre op *vs.* NSG: <0.01; SG pre op *vs.* RG: <0.01; SG 3 ds post op *vs.* NSG: <0.01; SG 3 ds post op *vs.* RG: <0.01; SG 3 mo post op *vs.* NSG: <0.01; SG 3 mo post op *vs.* RG: <0.01; SG 6 mo post op *vs.* NSG: <0.01; SG 6 mo post op *vs.* RG: <0.01	0.789 (95% CI: 0.647–0.930)	334.6 pg/mL Cr	88.2%	69%
Exoglycosidases (n=1; 2.6%)							
Taranta-Janusz *et al.* (16)	SG: n=16; NSG: n=16; RG: n=42	SG HEX: 0.76 pKat/µg Cr; SG HEX A: 0.19 pKat/µg Cr; SG HEX B: 0.46 pKat/µg Cr; SG FUC:0.27 pKat/µg Cr; SG GAL: 0.3 pKat/µg Cr; SG MAN:0.3 pKat/µg Cr; SG GLU: 0.31 pKat/µg Cr; NSG HEX: 0.51 pKat/µg Cr; NSG HEX A: 0.15 pKat/µg Cr; NSG HEX B: 0.33 pKat/µg Cr; NSG FUC:0.29 pKat/µg Cr; NSG GAL: 0.3 pKat/µg Cr; NSG MAN:0.33 pKat/µg Cr; NSG GLU: 0.28 pKat/µg Cr; RG HEX: 0.13 pKat/µg Cr; RG HEX A: 0.02 pKat/µg Cr; RG HEX B: 0.12 pKat/µg Cr; RG FUC: 0.08 pKat/µg Cr; RG GAL: 0.09 pKat/µg Cr; RG MAN: 0.1 pKat/µg Cr; RG GLU: 0.09 pKat/µg Cr	SG pre op *vs.* SG post op: <0.01; SG post op *vs.* NSG: NS; SG post op *vs.* RG: <0.01; SG HEX *vs.* NSG HEX: NS; SG HEX *vs.* RG HEX: <0.01; NSG HEX *vs.* RG HEX: <0.01; SG HEX A *vs.* NSG HEX A: <0.01; SG HEX A *vs.* RG HEX A: <0.01; NSG HEX A *vs.* RG HEX A: <0.01; SG HEX B *vs.* NSG HEX B: NS; SG HEX B *vs.* RG HEX B: <0.01; NSG HEX B *vs.* RG HEX B: <0.01; SG FUC *vs.* NSG FUC: NS; SG FUC *vs.* RG FUC: <0.01; NSG FUC *vs.* RG FUC: <0.01; SG GAL *vs.* NSG GAL: NS; SG GAL *vs.* RG GAL: <0.01; NSG GAL *vs.* RG GAL: <0.01; SG MAN *vs.* NSG MAN: NS; SG MAN *vs.* RG MAN: <0.01; NSG MAN *vs.* RG MAN: <0.01; SG GLU *vs.* NSG GLU: NS; SG GLU *vs.* RG GLU: <0.01; NSG GLU *vs.* RG GLU: <0.01	HEX: 0.869; HEX A: 0.846; HEX B: 0.858; FUC: 0.837; GAL: 0.798; MAN: 0.821; GLU: 0.814	HEX: 0.309 pKat/µg Cr; HEX A: 0.097 pKat/µg Cr; HEX B: 0.306 pKat/µg Cr; FUC: 0.2 pKat/µg Cr; GAL: 0.156 pKat/µg Cr; MAN: 0.204 pKat/µg Cr; GLU: 0.171 pKat/µg Cr	HEX: 93.8%; HEX A: 84.4%; HEX B: 68.8%; FUC: 81.3%; GAL: 87.5%; MAN: 87.5%; GLU: 84.4%	HEX: 76.2%; HEX A: 78.6%; HEX B: 90.5%; FUC: 81.0%; GAL: 71.4%; MAN: 76.2%; GLU: 73.8%
CD10 (n=1; 2.6%)							
Gerber *et al.* (13)	SG: n=12; RG: n=12	SG: 8.94/Cr (mean); RG: 2.98/Cr	SG *vs.* RG: <0.01	ND	ND	ND	ND

Table 2 (*continued*)

Table 2 (*continued*)

Author	Study groups	Biomarker concentrations	Outcomes	AUC on ROC curve	BCU value	Sensibility	Specificity
CD13 (n=1; 2.6%)							
Gerber *et al.* (13)	SG: n=12; RG: n=12	SG: 10.84/Cr (mean); RG: 1.15/Cr	SG *vs.* RG: <0.05	ND	ND	ND	ND
CD26 (n=1; 2.6%)							
Gerber *et al.* (13)	SG: n=12; RG: n=12	SG: 978.57/Cr (mean); RG: 90.56/Cr	SG *vs.* RG: <0.01	ND	ND	ND	ND
α-GST (n=1; 2.6%)							
Bieniaś *et al.* (7)*	Group A: n=25; group B: n=11; group C: n=9; RG: n=21; ON: n=28; NON: n=17	Group A: 4.51 ng/mg Cr (median); group B: 6.17 ng/mg Cr; group C: 4.73 ng/mg Cr; RG: 1.11 ng/mg Cr	Group A *vs.* control group: 0.0001; group B *vs.* control group: 0.008; group C *vs.* control group: 0.008; ON *vs.* NON: 0.03	ON *vs.* RG: 0.902; ON *vs.* NON: 0.750	ON *vs.* RG: 0.046 ng/mg Cr; ON *vs.* NON: 0.098 ng/mg Cr	ON *vs.* RG: 81.8%; ON *vs.* NON: 84.6%	ON *vs.* RG: 84.6%; ON *vs.* NON: 69.2%
Π-GST (n=1; 2.6%)							
Bieniaś *et al.* (7)*	Group A: n=25; group B: n=11; group C: n=9; RG: n=21; ON: n=28; NON: n=17	Group A: 30.4 ng/mg Cr (median); group B: 17.9 ng/mg Cr; group C: 16.3 ng/mg Cr; RG: 14.6 ng/mg Cr	Group A *vs.* control group: 0.03; group B *vs.* control group: ns; group C *vs.* control group: NS; ON *vs.* NON: NS	ON *vs.* RG: 0.3; ON *vs.* NON: 0.574	ON *vs.* RG: 0.082 ng/mg Cr; ON *vs.* NON: 0.103 ng/mg Cr	ON *vs.* RG: 92.3%; ON *vs.* NON: 92.3%	ON *vs.* RG: <1%; ON *vs.* NON: 7.7%
IL6 (n=1; 2.6%)							
Yu *et al.* (5)	UPJO: n=17; RG: n=17	ND	UPJO *vs.* RG: <0.0073; bilateral UPJO *vs.* unilateral UPJO: <0.007; bilateral UPJO *vs.* RG: <0.03	0.78	ND	ND	ND
BD1 (n=1; 2.6%)							
Gupta *et al.* (8)	SG: n=30; RG: n=15	SG: 109.10 ng/mg Cr (median); RG: 206.40 ng/mg Cr	SG *vs.* RG: 0.015	0.73	152.8 ng/mg Cr	71.4%	80.8%
Cathelicidin (LL37) (n=1; 2.6%)							
Gupta *et al.* (8)	SG: n=30; RG: n=15	SG: 1.8 ng/mg Cr (median); RG: 5.34 ng/mg Cr	SG *vs.* RG: 0.0007	0.80	2.599 ng/mg Cr	80%	76.7%
HIP/PAP (n=1; 2.6%)							
Gupta *et al.* (8)	SG: n=30; RG: n=15	SG: 0.03 ng/mg Cr (median); RG: 0.07 ng/mg Cr	SG *vs.* RG: 0.0461	0.68	0.033 ng/mg Cr	53.3%	86.7%
HD5 (n=1; 2.6%)							
Gupta *et al.* (8)	SG: n=30; RG: n=15	SG: 0.24 ng/mg Cr (median); RG: 0.36 ng/mg Cr	SG *vs.* RG: NS	ND	ND	ND	ND
Trx (n=1; 2.6%)							
Xu *et al.* (12)	SG: n=156; RG: n=80	ND	SG *vs.* RG: <0.001	ND	SRF <39.2%: 21.3 ng/mL; APD >30 mm: 22.1 ng/mL; grade IV HN: 27.1 ng/mL	85.9%; 78.2%; 66.2%	64.1%; 66.7%; 75.0%
Semaphorin 3A (n=1; 2.6%)							
Li *et al.* (9)	SG: n=42; NSG: n=42; RG: n=44	SG pre op: 256.1 pg/mg Cr (median); SG pelvis: 391.5 pg/mg Cr; SG 1 mo post op: 166.6 pg/mg Cr; NSG: 82.1 pg/mg Cr; RG: 48.1 pg/mg Cr	SG pre op *vs.* NSG: <0.01; SG pelvis *vs.* NSG: <0.01; SG pre op *vs.* RG: <0.01; SG pelvis *vs.* RG: <0.01; SG 1 mo post op *vs.* NSG: <0.05; SG 1 mo post op *vs.* RG: <0.01	0.825 (95% CI: 0.691–0.960)	186.65 pg/mg Cr	89.5%	80%
L-FABP (n=1; 2.6%)							
Noyan *et al.* (17)	SG: n=26; NSG: n=36; RG: n=20	SG: 1.2 ng/mg Cr [0–15] (median); NSG: 1.5 ng/mg Cr [0–11]; RG: 0.8 ng/mg Cr [0–7]	SG *vs.* NSG: NS; SG *vs.* RG: NS	ND	ND	ND	ND
Netrin 1 (n=1; 2.6%)							
Li *et al.* (9)	SG: n=42; NSG: n=42; RG: n=44	SG pre op: 736.9 pg/mg Cr (median); SG pelvis: 822.7 pg/mg Cr; SG 1 mo post op: 604.6 pg/mg Cr; NSG: 488.5 pg/mg Cr; RG: 287.7 pg/mg Cr	SG pre op *vs.* NSG: <0.01; SG pelvis *vs.* NSG: <0.01; SG pre op *vs.* RG: <0.01; SG pelvis *vs.* RG: <0.01; SG 1 mo post op *vs.* NSG: <0.01; SG 1 mo post op *vs.* RG: <0.01	0.745 (95% CI: 0.577–0.914)	642.95 pg/mg Cr	73.7%	80%

Table 2 (*continued*)

Table 2 (*continued*)

Author	Study groups	Biomarker concentrations	Outcomes	AUC on ROC curve	BCU value	Sensibility	Specificity
Caspase 3 (n=1; 2.6%)							
Shirazi *et al.* (11)	SG: n=31; RG: n=33	SG pre op: 22.38 ng/mg Cr (mean); SG 3 mo post op: 13.90 ng/mg Cr; SG 6 mo post op: 8.34 ng/mg Cr	SG pre op *vs.* SG 3 mo post op *vs.* 6 mo post op: <0.01; SG pre op *vs.* RG: <0.001; SG 3 mo post op *vs.* RG: NS	ND	ND	ND	ND
TNFα (n=1; 2.6%)							
Shirazi *et al.* (11)	SG: n=31; RG: n=33	SG pre op: 80.00 pg/mg Cr (mean); SG 3 mo post op: 32.89 pg/mg Cr; SG 6 mo post op: 13.34 pg/mg Cr	SG pre op *vs.* SG 3 mo post op *vs.* 6 mo post op: <0.01; SG pre op *vs.* RG: <0.001; SG 3 mo post op *vs.* RG: NS	ND	ND	ND	ND
sFAS/APO-1 (n=1; 2.6%)							
Gawłowska-Marciniak *et al.* (25)	SG: n=45 (young children: n=7; older children: n=20; adolescents: n=18); RG: n=25 (young children: n=5; older children: n=5; adolescents: n=15)	SG pelvic urine young children 3.19 ng/mg Cr (mean); SG pelvic urine older children 3.17 ng/mg Cr; SG pelvic urine adolescents 1.06 ng/mg Cr; SG bladder urine young children 2.86 ng/mg Cr (mean); SG bladder urine older children 3.24 ng/mg Cr; SG bladder urine adolescents 1.0 ng/mg Cr; RG bladder urine young children 1.07 ng/mg Cr (mean); RG bladder urine older children 0.98 ng/mg Cr; RG bladder urine adolescents 0.33 ng/mg Cr; SG bladder urine young children 12 mo post op 1.45 ng/mg Cr (mean); SG bladder urine older children 12 mo post op 1.12 ng/mg Cr; SG bladder urine adolescents children 12 mo post op 0.98 ng/mg Cr	SG pelvic urine young children *vs.* RG bladder urine young children: <0.05; SG pelvic urine older children *vs.* RG bladder urine older children: <0.05; SG pelvic urine adolescents *vs.* RG bladder urine adolescents: <0.05; SG bladder urine young children *vs.* RG bladder urine young children: <0.05; SG bladder urine older children *vs.* RG bladder urine older children: <0.05; SG bladder urine adolescents *vs.* RG bladder urine adolescents: <0.05; SG bladder urine young children *vs.* SG bladder urine young children 12 mo post op <0.05; SG bladder urine older children *vs.* SG bladder urine older children 12 mo post op <0.05	ND	ND	ND	ND

Data were recorded according to the following categories: number of participants per category; urinary biomarker concentration; main outcomes investigated; value of the AUC on ROC curve; BCO value of urinary biomarker concentration; sensibility; specificity. *, The patients were divided into three subgroups A–C according to the open HN ultrasound grading system as follows: group A, renal pelvis and caliceal dilatation with mild to severe renal parenchymal loss; group B, renal pelvis and caliceal dilatation; group C, dilatation of renal pelvis alone. ON, obstructive nephropathy was defined as an impaired relative function of an obstructed kidney from 15 to 35% on nuclear medicine assessments. NON, non-obstructive nephropathy. #, Obstructive UPJO (O-UPJO): subjects who did not achieve T1/2 by the end of the test (T1/2 >20 minutes). Functional UPJO (F-UPJO): those who achieved T1/2 (T1/2, ≤20 minutes). Operative UPJO (OPER): all children who underwent a surgical procedure who had an obstructive slope curve and T1/2 more than 20 minutes. °, RG comprised of patients, who were considered for non-operative management, and experienced improvement in their condition during the course of follow-up. SG delayed comprised candidates for non-operative management of UPJO, however due to deterioration of the condition, pyeloplasty was indicated after a period of observation. SG early consisted of patients who required immediate pyeloplasty. AUC, area under the curve; CI, confidence interval; BCO, best cut-off value; ROC, receiver operating characteristic; ND, not determined; mo, months; wks, weeks; yrs, years; UPJO, ureteropelvic junction obstruction (without the definition of the treatment received); Obs, obstructed kidney, non-obs, healthy kidney; SG, surgical group; NSG, non-surgical group; RG, reference group; Preop, preoperatively; Intraop, intraoperatively; Postop, postoperatively.

MCP1

Several studies found that MCP1 levels were significantly increased in preoperative samples compared to healthy controls (10,15,24,29,42). Some authors (10,15,20,29) exhibited that MCP1 concentrations were greater in the surgical PUJO group compared to patients with mild non-obstructive hydronephrosis. Additionally, in the SG, the difference between the pre- and post-operative concentrations became significant lower between 2 and 4 months after surgery according to Grandaliano *et al.* (42).

EGF

Preoperative concentrations of urinary EGF were significantly increased compared to healthy controls according to Madsen *et al.* (24) and compared to children with dilated non-obstructed kidneys according to Mohammadjafari *et al.* (21). Conversely, data reported from Grandaliano *et al.* (42) showed significantly lower urinary EGF concentrations in the SG compared to healthy children and they were also significantly lower compared to the observational group according to Li *et al.* (28).

However, in the series reported by Taha *et al.* (39) no difference was identified between surgical patients and healthy children. Madsen *et al.* (24), Taha *et al.* (39) and Grandaliano *et al.* (42) considered the evolution of EGF concentrations after pyeloplasty: postoperative values decreased significantly between 2 and 4 months after surgery according to Grandaliano *et al.* (42), while no difference was reported by Madsen *et al.* (24) and by Taha *et al.* (39) 1 year after surgery.

KIM1

Preoperative values of KIM1 were reported significantly augmented compared to healthy controls by Karakus *et al.* (15) by Wasilewska *et al.* (32) and compared to conservative cases by Mohammadjafari *et al.* (21) and by Wasilewska *et al.* (32). Preoperative values of KIM1 were reported not significantly different compared to controls by Noyan *et al.* (17) Gerber *et al.* (13) and compared to conservative cases by Karakus *et al.* (15) and Noyan *et al.* (17).

CCL5/RANTES

Three studies analysed CCL5/RANTES as a promising biomarker of PUJO. According to Madsen *et al.* (24) and to Taranta-Janusz *et al.* (29) there was a significant difference between the CCL/RANTES concentration obtained from the pelvic urine of surgical PUJO patients and those obtained from the bladder of healthy children. This difference became insignificant postoperatively according to Madsen *et al.* (24) but not to Taranta-Janusz *et al.* (29).

CA19.9

Three studies (6,18,34) reported that preoperative CA19.9 values were significantly higher in the SG compared to the healthy RG. Atar *et al.* (18) also demonstrated that surgical PUJO patients have significantly higher preoperative values compared to dilated non-obstructive patients. Three months after surgery, the voided urine CA19.9 levels decreased significantly according to Atar *et al.* (18) and Kajbafzadeh *et al.* (34).

NAG

Two studies (36,37) stated that preoperative levels of NAG were significantly increased compared to the conservative cases. In addition, Taha *et al.* (37) demonstrated that younger children had significantly higher activities of voided urinary NAG compared to older ones at diagnosis.

Other markers

The other biomarkers were evaluated in two studies or less with different results and degrees of predicting success (See *Table 2*).

Discussion

Obstructive nephropathy represents the major cause of renal insufficiency in children and, among them, PUJO constitutes the most frequent condition (1). Currently, according to the European Association of Urology Guidelines, symptomatic obstruction, impaired DRF (less than 40%), decrease of more than 10% of renal function in subsequent investigations, poor drainage function after the administration of diuretic, increasing anteroposterior pelvic diameter (APD) on US, and grade III and IV hydronephrosis represent indications for surgery (43). However, in many cases, patients present border-line results that make difficult to predict whether the affected kidney is a risk of damage and, in some, the indication for surgery comes only after several radiological investigations,

often when the evidence that a renal damage has already established.

A biomarker has been defined as a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention (44). Animal model systems have provided new insights into the cellular response of the developing kidney to urinary tract obstruction, helping in identify molecules involved in the pathogenic response to kidney damage, mediators of interstitial inflammation, tubular apoptosis and fibrosis. They became targets of proteomic studies aiming to identify early predictors of renal sufferance that could be used for clinical decision-making, assisting in earlier and more reliable determination of patients at risk to develop renal damage, guiding more timely therapeutic decisions and monitoring the treatment efficacy.

In addition to their diagnostic relevance, they could also prove to be extremely useful in the designing molecular therapies to prevent or reverse the renal structural and functional consequences of obstructive nephropathy. We aimed to perform a systematic review of the published literature of urinary biomarkers used as a tool for diagnosis and prognosis of children with PUJO.

Analysis of the most used markers

NGAL

NGAL is a non-organ specific protein of the lipocalin family which is secreted by different tissues and is reabsorbed via epithelia endocytosis in the proximal renal tubules. Its expression is also induced in the thick ascending limb of Henle's loop and in the collecting ducts in response to renal tubular injury. Thus, the combination of increased gene expression in the distal nephron and altered reabsorption in the proximal tubule make it one of the first indicators of renal damage in case of obstruction. Case-control prospective studies in children with severe hydronephrosis secondary to PUJO suggested that urine NGAL/creatinine ratio from bladder was significantly higher in affected patients compared to normal subjects (5,7,8,15,17,26,32).

Although, Madsen *et al.* (30) didn't find any significant differences between bladder urine NGAL levels in PUJO patients and in controls, renal pelvis NGAL levels in obstructed kidneys were significantly higher than those in the bladder and the levels measured in the voided urine of healthy children. These data were confirmed by Cost *et al.* (26). NGAL levels tend to decrease at 3 to 6 months after surgery (15,30,32).

Finally, ROC curve was used to determine the BCO point of urinary NGAL levels in predicting PUJO patients and AUC and the corresponding 95% CI were calculated. The best performance was reported by Madsen *et al.* (30) who found at a cut off value of 20.57 ng/mg Cr, an AUC of 0.923 [95% confidence interval (CI), 0.837–1.000] which yielded 82% sensitivity and 100% specificity.

TGFβ1

TGFβ1 is a proinflammatory, proapoptotic, profibrotic cytokine and fibroblast chemoattractant which plays a major role in renal fibrosis, also via epithelial-mesenchymal transition. Up-regulation of TGFβ1 synthesis in the kidney is associated with accumulation of collagen and scarring, leading to the development of advanced chronic renal disease.

Experimental models documented that kidney responds to obstruction inducing a cascade of molecular events and histological changes starting from the up-regulation of the renin-angiotensin system, which increase the expression of tissue TGFβ1. The deduction is that its level could be used as a non-invasive tool to evaluate the progression of renal disease and to monitor the efficacy of surgery. TGFβ1 levels are remarkably elevated in surgical PUJO patients in confront to healthy children (23,35,39). Moreover, postoperative mean TGFβ1 concentration was significantly lower than preoperative TGFβ1, according to Sager *et al.* (35) and Taha *et al.* (39).

MCP1

MCP1 is a chemokine that promotes monocyte chemotaxis. In case of obstruction, its expression at the tubular level seems to be strictly associated with the recruitment of these inflammatory cells within the interstitial space. Thus, MCP1 urine excretion could be related to the extent of monocyte infiltration and the consequent progression of interstitial renal fibrosis.

All studies agreed in considering MCP1 levels highly related to the extent of tubular atrophy and interstitial fibrosis and demonstrated that its urinary concentration could successfully discriminate not only between children who require an intervention and healthy controls but also within the hydronephrosis group. In fact, various authors found that MCP1 urinary levels are significantly increased in surgical patients compared to healthy controls (5,10,15,24,29,42) and compared to children managed conservatively (10,15,20,29).

MCP1 could be used for long term follow-up in the postoperative period since its levels decreased and became similar to the healthy group between 2 and 4 months after surgery (15,24,42). Analysing the ROC curves, MCP1 maintained also a good diagnostic profile and therefore may be used to distinguish surgical PUJO patients.

EGF

EGF is a polypeptide growth factor which plays a fundamental role in normal tubulogenesis. It is synthesized by the ascending portion of Henle's loop and by the distal convoluted tubule and displays fundamental effects on intact glomeruli, proximal tubules and collecting ducts. It was demonstrated that it has a central role in modulating tubular cell growth and tissue response in kidneys with tubule interstitial injury. However, the evaluation of urinary EGF concentration in PUJO children is still not fully understood and the studies that have investigated its urinary expression described contradictory results. This could be due to the fact that different methods were used in the studies: two studies considered also patients with bilateral disease, two reported also the concentration of the biomarker collected from the pelvic urine and two studies compared the urinary level of children with surgical PUJO with children with dilated but non-obstructed kidneys. Particularly, EGF urinary levels in patients undergoing surgery were significantly higher compared to those treated conservatively in the study of Mohammadjafari *et al.* (21) but they were significantly lower in the study of Li *et al.* (28). Although Grandaliano *et al.* (42) claimed that the preoperative concentrations of urinary EGF were significantly reduced in PUJO patients in comparison to their healthy controls, Madsen *et al.* (24) found that they were more elevated. To further confuse the situation, Taha *et al.* (39) reported that there was no significant difference of EGF values between surgical patients and controls and moreover there was no significant difference between preoperative and postoperative values even 1 year after surgery. In conclusion, the role of EGF as a urinary marker of PUJO seems, at least, debatable.

KIM1

KIM1 is a member of the type I transmembrane glycoprotein. Since it is undetectable in healthy children but is strongly expressed and released by damaged proximal tubular epithelial cells until complete recovery, it could be utilised as an early and sensitive biomarker for kidney injury in the setting of obstructive nephropathy.

In this scenario, several clinical studies have shown that urinary KIM1 is higher in patients with PUJO compared to control groups (15) and to children with mild hydronephrosis (21,32). However, other studies failed in identifying differences between PUJO patients and healthy controls (13,17) or hydronephrotic patients (15,17). KIM1 levels have a tendency to decrease and normalize by 3 months after surgery (15,32). ROC analyses were performed to define the diagnostic profile of KIM1 in identifying children with an obstructed kidney condition with quite good results. The best AUC (0.89) was reported by Karakus *et al.* (15) with a cut-off value of 0.687 ng/mg Cr, which gave a sensibility of 92.3% and a specificity of 83.3%. It is, furthermore, possible to conclude that KIM1 urinary levels are closely related to the severity of renal damage, since a negative correlation was found with DRF in radionuclide scans (32). However, Gerber *et al.* (13) didn't identify any significant linear correlations. This could have been consequence of the small sample size of their study or the presence of outliers in their small datasets, making any potential correlations difficult to demonstrate. No significant correlation was found with initial anterior posterior (AP) diameter (length) of the pelvis.

Critical review

Recently much has been learned about the pathophysiology of obstructive nephropathy and many novel biomarkers have been investigated for diagnostic and prognostic purposes. A number of endogenous molecules have been identified with different degrees of success, often with contradictory results. This wide range of outcomes could be due to a variety of reasons. First of all, the populations considered in the different articles were quite heterogeneous. Secondly, the heterogeneity of the populations considered and the different criteria adopted to classify patients made virtually impossible to compare the results. In addition to this, also the study designs were extremely wide-ranging. Another important bias was that these studies were held utilizing a wide range of patient ages. Elder children could therefore have suffered from ureterovascular hydronephrosis due to aberrant renal vessels. In these cases, decrements in renal function may occur discontinuously, inevitably interfering only episodically with urinary biomarker concentrations, which decrease during the diuretic phase of the renal impairment. In addition, it is also possible that

the progression of the histopathological tubulointerstitial changes is extremely different between the age groups. Finally, the duration of follow-up was quite short especially in the more recent studies. All these shortcomings could be overcome by large prospective clinical trials with appropriate and strictly design protocols.

Urinary biomarkers have been extensively used as a promising tool for non-invasive assessment of PUJO in children. They could be helpful not only in the diagnosis of congenital obstructive uropathies but also in the differentiation between dilated but non-obstructed kidneys that could be managed conservatively.

Some studies also demonstrated that the urinary biomarkers could be useful in the evaluation of the surgical treatment success. Nevertheless, the existing literature is still lacking of solid and definitive studies. Large multicentre and carefully designed prospective studies are needed to evaluate the clinical usefulness of urinary biomarkers in the diagnosis and follow-up of children with obstructive nephropathy.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tau.2020.01.01). NRD and CT report other from SpOtOn Clinical Diagnostics Ltd, NRD and CT have a patent Stable isotope albumin peptide internal standard issued. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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