J Pediatr Rev. 2016 July; 4(2):e7567. doi: 10.17795/jpr-7567.

Published online 2016 July 27. **Review Article**

The Role of Urinary Biomarker Levels in Assessing the Presence and Severity of Ureteropelvic Junction Obstruction in Children: A Systematic Review and Meta-Analysis

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Received 2016 June 15; **Revised** 2016 July 05; **Accepted** 2016 July 12.

Abstract

Context: Ureteropelvic junction obstruction (UPJO) is the most common obstructive disease of the urinary tract in infancy and childhood with a prevalence of 15% - 45% in neonates with antenatal hydronephrosis. The diagnosis of UPJO should be confirmed by imaging studies - most of which have a propensity to radiation exposure.
Objectives: The current study aimed to present a review protocol to assess the role of measuring urinary biomarkers to distinguish severe UPJO from milder forms of the disease.
Data Sources: The database of UPJO studies was searched and studies that compared the levels of urinary biomarkers with the gold standard (i e, dynamic renal scans) for UPJO diagnosis were selected. Severity assessment was done quantitatively.
Study Selection: Three hundred fifty-eight articles were identified across the electronic databases. Twenty-seven articles were selected for the final analyses.
Data Extraction: Data were extracted independently by three reviewers and analyzed using STATA software version 12.
Results: Meta-analysis of studies showed that patients with severe UPJO had significantly higher biomarker levels than those with mild to moderate obstruction, with a pooled standardized mean difference (SMD) of 0.5 (confidence interval (CI) 95%, 0.34 - 0.67; $P < 0.001$); and significantly higher biomarker standardized to urinary creatinine levels than those with mild to moderate obstruction, with a pooled SMD of 1.02 (95% CI, 0.88 - 1.16; $P < 0.001$). Meta-analysis showed that patients with severe UPJO had significantly higher biomarker levels than healthy children, with a pooled SMD of 1.27 (CI 95%, 1.16 - 1.39; $P < 0.001$); and significantly higher biomarker standardized to urinary creatinine levels than healthy children, with a pooled SMD of 1.14 (CI 95%, 0.95 - 1.32; $P < 0.001$).
Conclusions: The assessment of urinary biomarkers is a helpful tool to assess the presence and severity of UPJO, but there is little published data on each of the studied biomarkers. It is suggested to perform future larger multicenter studies.

Keywords: Urinary Biomarker, Ureteropelvic Junction Obstruction, Children, Systematic Review and Meta-Analysis

1. Context

Ureteropelvic junction obstruction (UPJO) is the most common obstructive disease of the urinary tract in infancy and childhood. With widespread obstetric sonographic imaging, the diagnosis and incidence of UPJO increased significantly (1). The incidence of UPJO in infants with antenatal history of hydronephrosis was reported 15% - 45% (2). The high incidence and the frequency of antenatal hydronephrosis, which is 0.5% - 2%, reveal the significance of UPJO as a common problem in pediatric urology. The diagnosis of UPJO should be confirmed by imaging studies: ultrasound, excretory urogram and dynamic renal scans (3). The dynamic renal scans such as MAG3 show the severity of obstruction and differential renal function. The scintigraphic findings help clinicians choose the best treatment strategies. Most infants with milder forms of UPJO need no surgical treatment and benefit from supportive care. Surgical correction indicates more severe forms, especially those with renal functional impairment or symptomatic complications. Therefore, imaging studies should be performed to plan the best therapy. The imaging studies have some limitations: they expose children to radiation and show lower accuracy during the first few weeks of life due to the physiologically low glomerular filtration rate (GFR) (4). These limitations lead researchers to study newer alternative modalities without such difficulties. Urinary biomarkers are recent candidates for alternative diagnostic modalities studied widely. The current study aimed to evaluate the relationship between biomarkers and severity of obstructions (5-11).

Twenty-six biomarkers were candidates for such assessment. The proposed mechanisms of action for such biomarkers were summarized in four groups (Table 1): 1) Collagen synthesis and growth factors (transforming growth factor (TGF), epidermal growth factor (EGF), EMMPRIN, matrix metalloproteinase-9 (MMP9), tissue inhibitor of metalloproteinase-1 (TIMP-1), procollagen, angiotensinogen); 2) Inflammatory response (monocyte chemoattractant protein-1 (MCP-1), interleukin-6 (IL-6), tumor necrosis factor (TNF), RANTES, gamma-glutamyl transferase (GGT), chemokine (C-C motif) ligand 5 (CCL5), saturated fatty acids (SFAs); 3) cellular damage (endothelin-1 (ET-1), N-acetylmuramide glycanhydrolase (NAG), neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule-1 (KIM-1), cyst-c, FAB); and 4) Others (Carbohydrate Antigen (CA) 19-9, alkaline phosphatase (Alkp) (Table 1) (12-35).

2. Objectives

Since studies published for such markers were numerous and had conflicting results, review protocol was planned to assess the role of measuring urinary biomarkers to distinguish severe UPJO from milder forms of the disease in patients under 16 years old, i e, from birth to adolescence.

3. Data Sources

Studies on UPJO published up to the end of 2014 were evaluated. The inclusion criteria were: focusing on the diagnosis of UPJO or on distinguishing its severity in patients less than 16 years old using any biomarker. Medline, CAB Abstracts, Embase, Web of Science, the Cochrane Library, and Google Scholar were systematically searched using appropriate text words and thesaurus terms for papers relating to the following: any biomarker names and their synonyms or acronyms; UPJO and its synonyms; antenatal hydronephrosis, its synonyms and acronyms and the limitation ages for neonate, infant, child, or adolescent; but with no limitations on date or geographical location. Searches were also undertaken using reference lists from these papers, the authors' own collections and review articles. The enrolled studies compared the urinary biomarkers with the gold standard of dynamic renal scans for UPJO diagnosis and severity assessment quantitatively.

4. Study Selection

Studies with narrative or descriptive assessment or with unknown case definitions were excluded from the study. Potentially relevant articles were identified according to the mentioned inclusion and exclusion criteria. The three main authors performed the article search. The search results obtained by each author were compared and the duplicate articles were omitted. The final articles were assessed for enrolment, first by title then by abstract, before retrieving the articles in full text. The subjects were tabulated based on the following criteria: location, date and type of study; name of author, age group, sample size, name of biomarker assayed and mean and standard deviation (SD) values of biomarkers. The methodology of selected studies was assessed according to QUADAS methodological quality criteria.

5. Data Extraction

The studies had diverse population and measuring assays. Regarding the population, some studies included children with severe UPJO and compared them with mild or moderate UPJO. Some studies compared healthy children or infants with the ones having UPJO. Other studies included patients from the three patient groups. The measurement of urinary biomarkers was presented as absolute concentration or the ratio of biomarker concentration to creatinine concentration. Relevant studies were stratified into subgroups for meta-analysis. First, the studies were stratified according to the following groups: normal, moderate obstruction, and severe obstruction; comparisons were then made between the following groups: severe obstruction vs. moderate obstruction and severe obstruction vs. normal state. Second, the data were stratified by biomarker level assessment: 1) direct biomarker level and 2) biomarker standardized to urinary creatinine level. For each of these subgroups, two main outcomes were considered: 1) mean and SD of biomarker levels for continuous data and 2) number of true positive, true negative, false positive, and false negative for dichotomous data. The mean and SD were estimated using the recommendations of Hozo et al. (36). For studies that reported the median and interquartile range solely and the standard deviation were estimated for studies that reported the percentiles solely according to the following formula:

$$\mathrm{SD} = \left| \frac{X1 - X2}{Z_{\frac{P2}{100}} - Z_{\frac{P1}{100}}} \right| \quad (1)$$

Where X1 and X2 are the two percentiles, P1 and P2 are the two percentages, and Z (P) is the standard normal deviate that has a tail area of P to the left. While the biomarker levels (continuous measurements) were measured in different units across the studies, SMD (Hedge's g) was used to combine the outcomes in the meta-analyses. The statistical heterogeneity of the studies was assessed through

Table 1. Biomarkers to Diagnose Ureteropelvic Junction Obstruction, Their Mechanism of Action and the Number of Studies Assessed Them

Name of Biomarker	Mechanism of Action	Number of Studies Performed (References)
Transforming growth factor-β_1 (TGF-β_1)	Plays a critical role in the regulation of collagen synthesis in the extracellular matrix	10 (9-18)
N-acetyl-beta-d-glucosaminidase (NAG)	A very sensitive marker of renal tubular impairment in various disease states	4 (19-22)
Neutrophil gelatinase associated lipocalin (NGAL)	A well-established biomarker of kidney injury	4 (23-26)
Epidermal growth factor (EGF)	Modulates epithelial cell growth and metabolism, and thereby mediates tubular regeneration after renal injury	3 (14, 27, 28)
Monocyte chemotactic peptide-1 (MCP-1)	Exerts strong chemoattractant activities on the monocytes, T cells, and natural killer cells	3 (22, 27, 29)
Kidney injury molecule 1 (KIM-1)	A sensitive and specific biomarker for proximal tubule injury	3 (23, 26, 28)
β_2-microglobulin (β_2 MG)	Detects acute kidney injury	2 (18, 25)
Endothelin-1 (ET-1)	A strong vasoconstrictor that is a mediator of vascular and cellular damage in the course of urinary system obstruction	2 (22, 30)
Osteopontin (OPN)	1-Mediates early interstitial macrophage influx and fibrosis	2 (25, 29)
	2- Functions as a survival factor for renal tubulointerstitial cells, where it suppresses apoptosis	
Alkaline phosphatase (Alkp)	An osseous enzyme	2 (20, 21)
γ-glutamyl transferase (GGT)	Involved in the transfer of amino acids across the cellular membrane and leukotriene metabolism	2 (20, 21)
Carbohydrate Antigen 19-9 (CA-19)	A tumor marker of pancreatic carcinoma	1 (31)
Interleukin-6 (IL-6)	A pro-inflammatory cytokine	1 (10)
Tumor necrosis factor-α (TNF-α)	A pro-inflammatory cytokine	1 (10)
EMMPRIN	Increased production and concomitant decreased degradation of matrix metalloproteinases	1 (32)
Matrix metalloproteinase-9 (MMP-9)	Particularly degrades type IV collagen	1 (32)
Tissue inhibitor of metalloproteinase-1 (TIMP-1)	Inhibits MMP-9 and degrades collagen	1 (32)
CCL5	Induces interstitial inflammatory changes in various types of human glomerular diseases by activating the migration of cells	1 (13)
SFAs/Apo-1 (SFAs)	Can antagonize cell-surface Fas function and suppress apoptosis of cells by blocking the Fas ligand	1 (13)
RANTES	A chemokine from the βor CC subfamily, secreted by macrophages and T lymphocytes	1 (29)
Cystatin C (CyC)	An early detector of acute kidney injury	1 (25)
Procollagen III	Degradation product of collagen	1 (33)
Heme oxygenase	A marker of renal function in children with congenital hydronephrosis	1 (34)
Angiotensinogen	Stimulates the synthesis of TGF-β1 and collagen type IV in the obstructed kidney	1 (35)
FABP	Promotes the β -oxidation of fatty acids in the mitochondria or peroxisomes and increases renal tubular injury	1 (26)

the calculation of tau2 and I2. A random effects model was applied unless the I2 was < 25%, in which a fixed effects model was used. The possibility of publication bias was assessed through the Egger weighted regression test. The nonparametric trim and fill method was used to estimate the number of hypothetical studies that were missing due to possible publication bias using the metatrim command in STATA. Since there was insufficient information for dichotomous data, the studies without meta-analysis were compared, then estimated and reported the sensitivity (sen), specificity (spe), positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio (LR+), negative likelihood ratio (LR-), diagnostic odds ratio (DOR) and Youden's J Statistic. Data were analyzed using STATA software version 12.

6. Results

6.1. Description of Studies

In the beginning of the study selection phase, 358 articles were identified across the electronic databases. After removing the duplicates, 320 articles remained. A comprehensive evaluation of the titles and abstracts resulted in the exclusion of 224 articles, leaving 96 records. Review of full text articles led to the exclusion of 69 studies. At the end, 27 articles were selected for the final analyses. A flow chart detailing the process of identification, inclusion, and exclusion of the studies is shown in Figure 1.

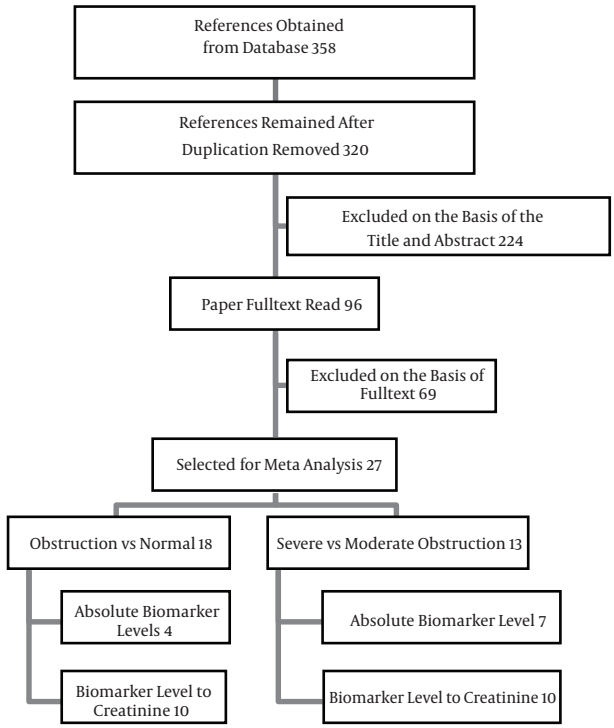

Figure 1. The Flow Chart of Assessment of Searched Articles

6.2. Study Characteristics

All articles but two were published from 2000 to 2014. The diversity of assessed biomarkers suggested that the results should be analyzed more individually. Twenty-five biomarkers were assessed; fourteen of them were reported only in one study, five of them in two studies, three in three studies and two in four studies. Only TGF-β1 was studied in ten papers. Therefore, the majority of the reported biomarkers did not have enough cases to be assessed separately. The total sample size was 1,584.

A summary of the descriptive characteristics for the included studies is given in Table 2. From the 27 articles, 13 articles studied only one distinct biomarker, two articles studied two biomarkers, eight articles and one article reported the levels of three and four biomarkers, respectively. The methods of the studies were homogeneous, and all had high methodological quality according to the quality assessment tool for diagnostic accuracy studies (QUADAS) methodological quality criteria, except for items 1 (i e, representativeness of the patients), 10 and 11 (i e, report of blinding) that were unclear. Almost all of the studies fulfilled at least 72.73% of the remaining QUADAS items (37) (Table 2).

6.3. Study Results

The studies assessed the accuracy of biomarkers in two ways. First, they distinguished severe obstruction with a need for pyeloplasty from mild to moderate hydronephrosis with no need to surgical intervention. Second, they compared patients with different degrees of hydronephrosis with healthy children. The value of biomarkers was also presented as two different measures: absolute biomarker concentration and the ratio of biomarker level to creatinine concentration. Therefore, the results were assessed as four demonstrations: absolute biomarker levels in patients with severe obstruction vs. the ones with mild to moderate obstruction (Figure 2), and the ratio of biomarker: creatinine levels in patients with severe obstruction vs. the ones with mild to moderate obstruction (Figure 3). To compare biomarker levels in patients with severe obstruction vs. the healthy children, two figures were shown: Figure 4 for absolute biomarker levels and Figure 5 for the ratio of biomarker: creatinine.

6.3.1. Biomarker Levels in Patients with Severe Obstruction vs. the Ones with Mild to Moderate Obstruction

6.3.1.1. Absolute Biomarker Levels

The meta-analysis of 14 studies showed that with a total sample size of 339, patients with severe obstruction

Table 2. Characteristics of the Studies Included in the Meta-Analysis

Name of the First Author (Reference Number)	Year of Study	Significance	Number of Subject (Total/Sever/Moderate/Healthy)	Biomarkers Assessed
ZIEG J (9)	2011	Sig	51/19/11/21	TGF-β1
Vasconcelos MA (10)	2011	(ALL Non sig	100/47/35/18	IL-6, TNF-α, TGF-β1
Sager C (11)	2009	(Sig)	38/19/0/19	TGF-β1
Taha M A (30)	2007	(Sig)	65/35/0/30	ET-1
Skalova S. (19)	2007	(Sig)	31/12/19/0	NAG
PALMER L. S. (12)	1997	(Non Sig)	32/13/0/19	TGF-β1
Cost N. G. (24)	2013	(Sig)	83/61/0/22	NGAL
Madsen M. G (27)	2013	(Both Sig)	41/28/0/13	EGF, hMCP-1
Kajbafzadeh A. M. (31)	2010	(Sig)	54/27/0/27	CA-19
Taha M A. (20)	2007	All (Sig)	50/35/15/0	NAG, Alkp, GGT
Li Z Z (18)	2012	(All Sig	44/22/0/22	β2-MG, TGF-β1
Rathod K. J. (21)	2012	All (Sig)	70/41/29/0	NAG, Alkp, GGT
Wasilewska A. (23)	2011	Both (sig)	65/20/20/25	NGAL, KIM-1
Mohammadjafari H (22)	2014	MCP-1, ET-1,NAG,ET-1/Cr, NAG/Cr (Non Sig) MCP-1/Cr (Sig)	42/24/18/0	MCP-1, ET-1,NAG
Tian F (32)	2015	All (Sig)	40/15/25/0	EMPRIM, MMP-9, TIMP1
Gawłowska-Marciniak A (13)	2013	All (Sig)	70/45/0/25	TGF-β1, CCL5, SfAs
Taranta-Janusz K (29)	2012	All (Sig)	55/15/21/19	MCP, Opn, RANTES
Madsen M G (25)	2012	β2-Mic & NGAL(Sig) , Ospn& Cyst-c (Non Sig)	37/24/0/13	β2-Mic ,NGAL, Opn, Cyst-c
Taha, M. A (14)	2007	TGF-β1 (Sig), EGF (NonSig)	65/35/0/30	TGF-β1, EGF
EL-SHERBINY M. T (15)	2002	(Sig)	26/15/11/0	TGF-β1
FURNESS P D (16)	1999	(Sig)	49/30/0/19	TGF-β1
Jianguo W. (33)	2014	(Sig)	89/29/30/30	Procollagen III
LiZZ (34)	2012	(Sig)	80/25/25/30	Heme oxygenase-1
LIATSIKOS E. N. (17)	2001	(Sig)	60/34/0/26	TGF-β1
Taranta-Janusz K. (35)	2013	(Sig)	70/31/20/19	Angiotensinogen
Mohammadjafari H. (28)	2014	Both (Sig)	59/24/18/17	EGF, KIM-1
Xie Y (26)	2014	All (Sig)	118/69/21/28	NGAL, KIM-1,FABP

Abbreviations: TGF-β1, transforming growth factor- β1; IL-6, interleukin-6; TNF-α, tumor necrosis factor-α; ET-1, endothelin-1; NAG, N-acetylmuramide glycanhydrolase; NGAL, neutrophil gelatinase-associated lipocalin; EGF, epidermal growth factor; MCP-1, monocyte chemoattractant protein-1; CA-19, carbohydrate Antigen 19 ; Alkp, alkaline phosphatase; GGT, gamma-glutamyl transferase; KIM-1, kidney injury molecule-1; MMP-9, matrix metalloproteinase-9; TIMP-1, tissue inhibitor of metalloproteinase-1; SfAs, saturated fatty acids; Opn, osteopontin.

had significantly higher biomarker levels than the ones with mild to moderate obstruction, with a pooled SMD of 0.5 (95% CI, 0.34 - 0.67; P < 0.001) (Figure 2). Funnel plots showed evidence of asymmetry (not shown here), and there was evidence of bias using the Egger (weighted regression) method (P for bias = 0.012). The estimate of SMD remained significant when the trim-and-fill procedure was used to correct the publication bias. Adjustment for publication bias according to Duval and Tweedie's trim and fill procedure resulted in a SMD of 0.34 (95% CI 0.18 - 0.51; P < 0.001) with the 2 imputed studies.

6.3.2. Biomarker Standardized to Urinary Creatinine Levels

The meta-analysis of 20 studies, with a total sample size of 527, showed that patients with severe obstruction had significantly higher biomarker standardized to urinary creatinine levels than the ones with mild to moderate obstruction, with a pooled SMD of 1.02 (95% CI, 0.88 -

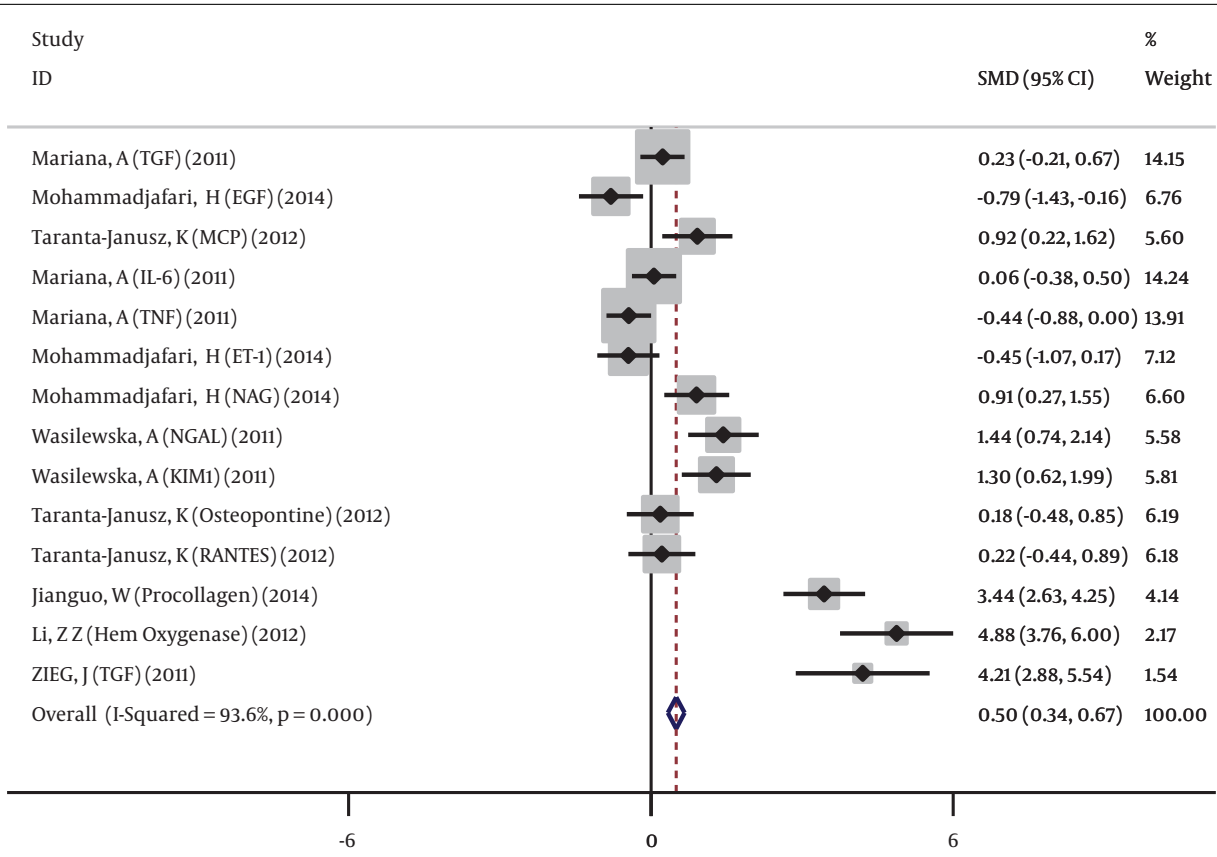

Figure 2. Biomarker Levels in Patients with Severe Obstruction vs. the ones with Mild to Moderate Obstruction

1.16; P < 0.001) (Figure 3). Funnel plots showed evidence of asymmetry (not shown here), and there was evidence of bias using the Egger (weighted regression) method (P for bias = 0.009). The estimate of SMD remained significant when the trim-and-fill procedure was used to correct the publication bias. Adjustment for publication bias according to Duval and Tweedie's trim and fill procedure resulted in a SMD of 0.52 (95% CI 0.4 - 0.65; P < 0.001) with six imputed studies.

6.3.3. Biomarker Levels in Patients' Severe Obstruction vs. Healthy Children

6.3.3.1. Absolute Biomarker Level

The meta-analysis of 32 studies, with a total sample size of 996, showed that patients with severe obstruction had significantly higher biomarker levels than healthy children, with a pooled SMD of 1.27 (95% CI, 1.16 - 1.39; P < 0.001) (Figure 4). Funnel plots showed evidence of asymmetry (not shown here), and there was evidence of bias using the Egger (weighted regression) method (P for bias = 0.001). The estimate of SMD remained significant when the trim-and-fill procedure was used to correct the publication bias. Adjustment for publication bias according to Duval and Tweedie's trim and fill procedure resulted in a SMD of 0.89 (95% CI 0.76 - 1.004; P < 0.001) with seven imputed studies.

6.3.4. Biomarker Standardized to Urinary Creatinine Levels

The meta-analysis of 15 studies, with a total sample size of 482, showed that patients with severe obstruction had significantly higher biomarker standardized to urinary creatinine levels than healthy children, with a pooled SMD of 1.14 (95% CI, 0.95 - 1.32; P < 0.001) (Figure 5). Funnel plots showed evidence of asymmetry (not shown here), and there was evidence of bias using the Egger (weighted regression) method (P for bias < 0.001). The estimate of SMD remained significant when the trim-and-fill procedure was used to correct the publication bias. Adjustment of publication bias according to Duval and Tweedie's trim and fill procedure resulted in a SMD of 0.72 (95% CI 0.54 - 0.9; P < 0.001) with 4 imputed studies.

Association between high level of biomarkers and obstruction (severe obstruction vs. mild to moderate obstruction)

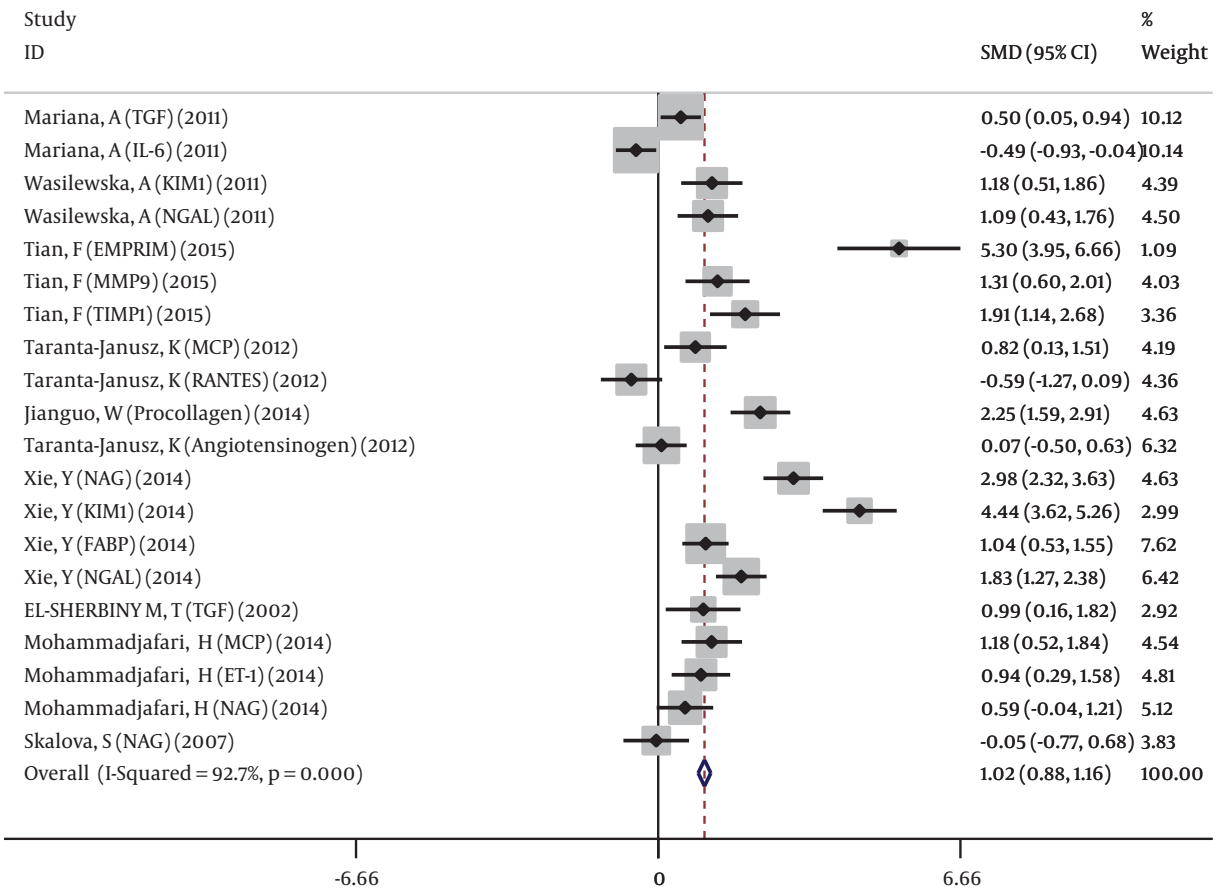

Figure 3. Biomarker Standardized to Urinary Creatinine Levels in Patients with Severe Obstruction vs. the Ones with Mild to Moderate Obstruction

The combined biomarkers were assessed in six studies (Table 3). From these six studies, only two reported excellent sensitivity and specificity for clinical use.

Association between high level of biomarkers and obstruction (sever obstruction vs. normal state). The combined biomarkers were assessed in three studies (Table 4). From these three studies, only one reported excellent sensitivity and specificity for clinical use (11).

7. Discussion

The method in assessing the severity of UPJO is a common dilemma in pediatric nephrology. The papers with topics on the relationship between urinary biomarker levels and the diagnosis and severity of UPJO were analyzed. Twenty-seven articles fulfilled the inclusion criteria. More than half of the papers were studies on more than one biomarker and each biomarker assessment was considered as a district study. The number of studies published for the majority of biomarkers was too small to be assessed separately. Therefore, subgroup analysis was not performed.

7.1. The Comparison Between Severe and Milder Forms of Hydronephrosis

The difference was significant on both the absolute biomarker level and the ratio of biomarkers to creatinine level. Out of the fourteen biomarkers that measured the absolute urinary levels of biomarkers, eight biomarkers were assessed, which showed that the biomarker levels were significantly higher in severe obstruction than in milder forms of hydronephrosis. Three studies revealed relatively different patterns with significantly higher SMD. The study by Zieg involved 19 children with obstructive uropathy (OU), 11 children with nonobstructive uropathy (NOU), and 21 healthy children, which showed that the mean urinary TGF-β1 concentrations in patients with OU were significantly higher than those of the ones with NOU (4.14 ± 0.67 vs. 1.80 ± 0.24 pg/mM creatinine, respectively,

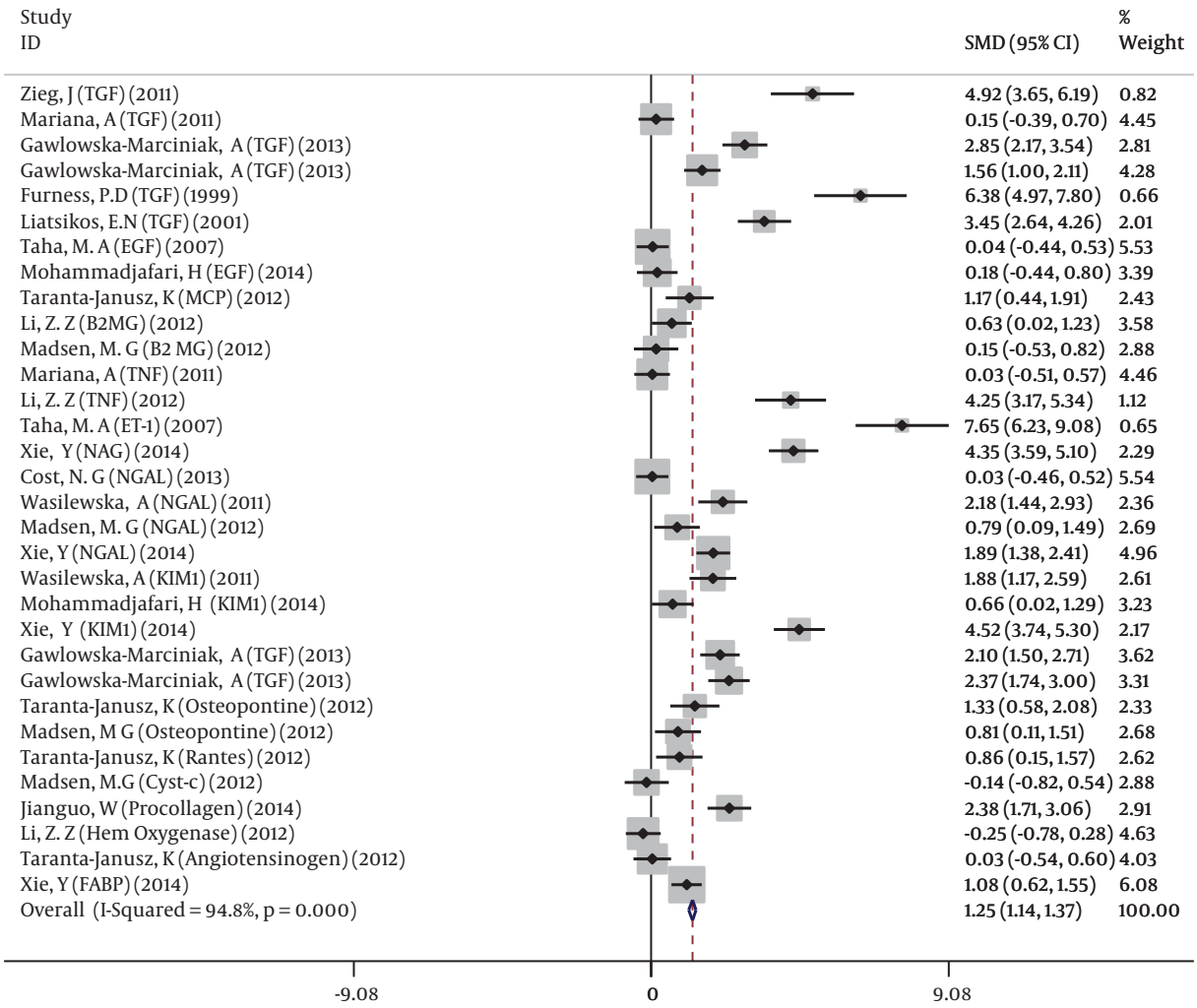

Figure 4. Biomarker Levels in Patients with Severe Obstruction vs. the Healthy Children

Table 3. Diagnostic Testing Accuracy, Measurements for Combined Biomarkers in Assessment of Obstruction

Author	Biomarker	TP (N)	FP (N)	FN (N)	TN (N)	Prevalence	Sensitivity	Specificity	PPV	NPV	LR+	LR-	DOR	The Youden J Statistic
Taha M. A (20)	NAG	34	3	1	12	70	97.14	80	91.89	92.31	4.86	0.04	136.00	0.77
Taha M.A (20)	Alp PHP	22	0	13	15	70	62.86	100	100	53.57	∞	0.37	∞	0.63
Taha M. A (20)	GGT	32	0	3	15	70	91.43	100	100	83.33	∞	0.09	∞	0.91
Rathod K. J. (21)	NAG	33	5	7	23	58.82	82.50	82.14	86.84	76.67	4.62	0.21	21.69	0.65

Abbreviations: PPV, positive predictive value; NPV, negative predictive value; LR+ positive likelihood ratio; LR-, negative likelihood ratio, DOR, diagnostic odds ratio; NAG, N-acetylmuramide glycanhydrolase; Alp, alkaline phosphatase; PHP, ; GGT, gamma-glutamyl transferase.

$P < 0.05$) and healthy controls (1.66 ± 0.28 pg/mM creatinine, $P < 0.05$) (1). Li studied 80 children categorized into three groups: one study group included twenty-five children (nineteen boys and six girls; mean age: 2.37 ± 0.66 years) with severe hydronephrosis (HN) due to unilateral, critical-degree ureteral stenosis, who underwent pyeloplasty; the first control group (control 1) included twenty-five children with mild, non-obstructive HN (seventeen boys and eight girls; mean age: 7.13 ± 0.65 years) who did not require pyeloplasty; and the second con-

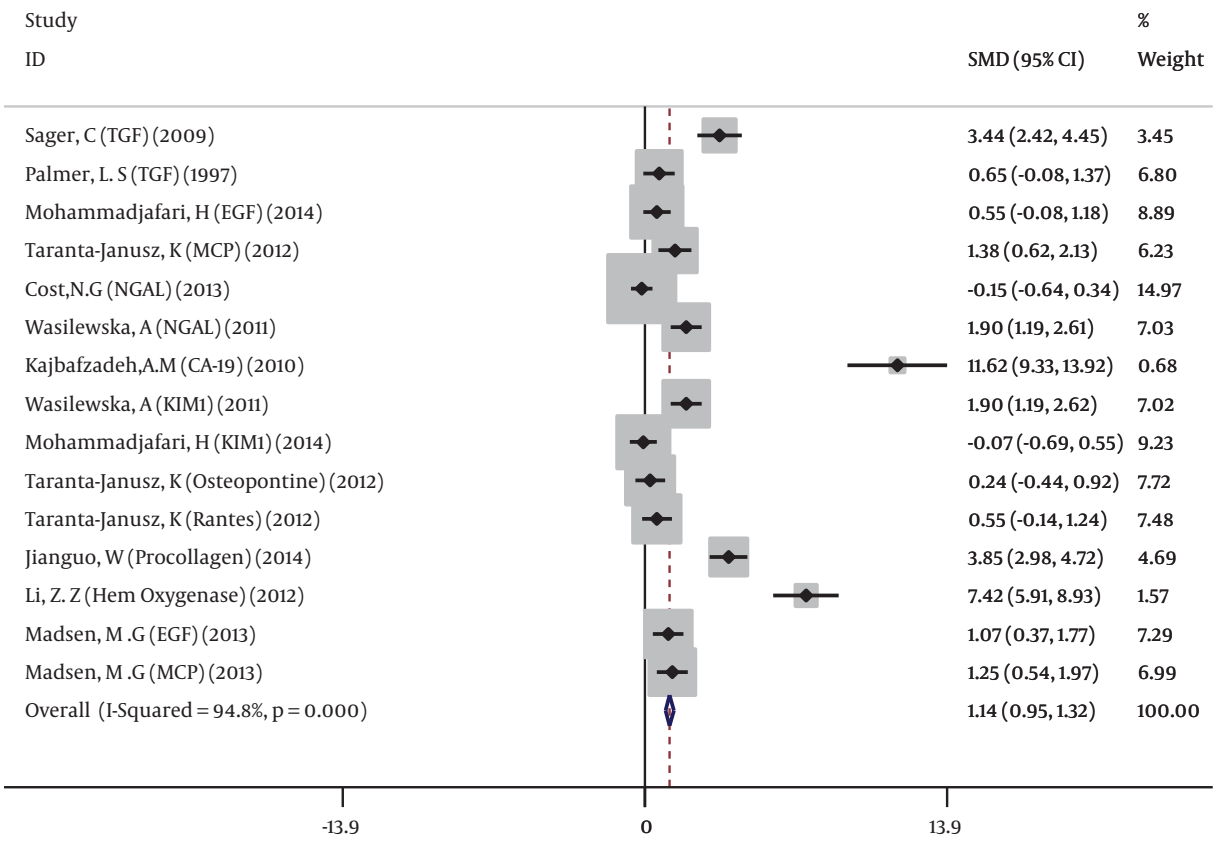

Figure 5. Biomarker Standardized to Urinary Creatinine Levels in Patients with Severe Obstruction vs. Healthy Children

Table 4. Diagnostic Testing Accuracy, Measurements for Combined Biomarkers in Assessment of Obstruction

Author	Biomarker	TP (N)	FP (N)	FN (N)	TN (N)	prevalence	Sensitivity	Specificity	PPV	NPV	LR+	LR-	DOR	The Youden Statistics
Madsen G. (27)	EGF	19	4	8	9	67.5	70.37	69.23	82.61	52.94	2.29	0.43	5.34	0.40
Madsen M.G (27)	MCP	21	4	6	9	67.5	77.78	69.23	84	60	2.53	0.32	7.88	0.47
Kajbafzadeh, A. M (31)	CA-19	27	7	0	33	40.3	100	82.5	79.41	100	5.71	0.00	∞	0.83

Abbreviations: PPV, positive predictive value; NPV, negative predictive value; LR+ positive likelihood ratio; LR-, negative likelihood ratio, DOR, diagnostic odds ratio; EGF, epidermal growth factor; MCP, monocyte chemoattractant protein; CA-19, carbohydrate antigen-19.

trol group (normal control) consisted of 30 healthy children (16 boys and 14 girls; mean age: 5.95 ± 0.70 years). They showed that the urinary heme oxygenase-1 (uHO-1) and uHO-1/creatinine (cr) levels before surgery and during surgery were significantly greater in the study group (2.04 ± 0.33 ng/mL) than in the control 1 (0.84 ± 0.11 ng/mL) and the normal control (0.36 ± 0.06 ng/mL) ($P < 0.01$). One month after surgery, uHO-1/cr decreased significantly in the study group compared with that of before surgery ($P < 0.01$), but was still higher than that of the control 1 ($P < 0.05$). The uHO-1 and uHO-1/cr levels were markedly lower in the normal control than that of the control 1 group ($P < 0.01$, $P < 0.05$, respectively) (10). Jianguo measured the procollagen III level in three groups of patients: twenty-nine children with severe unilateral obstruction who underwent pyeloplasty (group 1), 30 children with mild non-obstructive hydronephrosis (group 2), and 30 healthy children. He showed that the urinary levels were significantly higher in group 1 (390.6 pg/mL) than group 2 and control (127.8 and 120.2 pg/mL, respectively) (27). The three studies had the same methodological protocol as others but two of them assessed new biomarkers. It is not obvious that future studies have the same results. The ratio of urinary biomarker level to creatinine level was assessed 20 times in 10 studies. The current analysis revealed that the values were higher in severe groups than

in milder forms. A relatively different pattern with significantly higher SMD was reported by Tian, who studied 40 children in a follow up period of 24 months; 25 children had non-obstructed hydronephrosis, while 15 children had obstructed hydronephrosis. The urinary EMMPRIN level in the non-obstructive groups (33.7; ranged: 26.2-38.9 ng/mg cr) was significantly lower than that of the obstructed group (49.3; ranged: 46.5-55.7 ng/mg cr) (26). The methodologic approach of the authors was different - they followed the bases with babies with hydronephrotic conservatively, and then put patients in two groups based on renal function deterioration. Therefore, the net and end points of obstruction were assessed.

7.2. The Comparison Between Patients with Any Forms of Hydronephrosis and Normal Healthy Children

The difference was significant in both the absolute biomarker level and the ratio of biomarker to creatinine level. The absolute urinary biomarker level was assessed 34 times in 14 studies. It was found that the biomarker levels were significantly higher in children with hydronephrosis than in healthy children. The difference was very high in two distinct studies. Furness assessed the urinary levels of TGF-β1 in 30 patients, with a median age of five months old, who underwent surgery for obstruction and compared them with those in controls. It was reported that the mean bladder urine TGF-β1 was four fold higher in patients with upper tract obstruction than in controls (195 ± 29 vs. 47 ± 7 pg/mg creatinine, $P < 0.001$) (14). Taha examined the role of voided urine ET-1 levels during the diagnosis and follow up of UPJO, and included 35 children with unilateral UPJO who underwent pyeloplasty and 30 control groups, each one including 10 healthy children. The preoperative ET-1 level was significantly higher in the study group than all the control groups (23). The method of the study was not different in the two mentioned studies and the reason for the relatively different results was not obvious. Ten reports on 15 biomarkers, which measured the ratio of the urinary levels of biomarkers to creatinine concentration, were analyzed. It was found that the biomarker levels were significantly higher in children with hydronephrosis than the normal ones. Kajbafzadeh studied a unique tumor marker, carbohydrate antigen (CA) 19-9, and concluded that the biomarker was a valuable adjunctive tool in decision making for the surgical treatment of UPJO. He included 27 children with unilateral UPJO who underwent pyeloplasty and 27 children in the healthy control group. The preoperative CA 19-9 level was significantly higher in the study group (19.1 ± 2.17) than the control group (7.1 ± 1.53) $P < 0.001$ (24). Limitations of the study: The obvious limitation of the study was the relative diversity of biomarkers assessed and the scarcity of studies performed for each marker. Most biomarkers in different studies could not be compared, but a mixture of different studies with several biomarkers had to be reported.

8. Conclusion

The assessment of urinary biomarkers was a helpful tool to assess the presence and severity of UPJO. The measurement could be performed as absolute biomarker concentrations and their ratio to creatinine. Despite good results, most biomarkers were studied by only one or two researchers with a small sample size. There were few published data on each of them. Therefore, with the promising background, it is suggested to perform future larger multicentered studies. This idea is especially true for the 14 biomarkers that were studied only once.

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