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Review Article

Pop-off mechanisms as renoprotective mediators in children with posterior urethral valves: A systematic review and meta-analysis

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Summary

Background
Pop-off mechanisms are potential pressure-relieving mediators in patients diagnosed with posterior urethral valves (PUV). This systematic review aimed to synthesize the existing evidence regarding the protective effect of pop-off mechanisms on renal function in children with PUV.

Methods
We conducted a systematic review of the literature that involved an extensive search in the main databases of the medical bibliography. Three independent reviewers selected the relevant articles. Methodological quality was rated using the Newcastle Ottawa Scale index. We used random meta-analyses to compare different outcomes (serum creatine, Nadir serum creatinine, and Chronic Kidney Disease) between children with PUV and pop-off mechanisms and those with PUV without pop-off mechanisms.

Results
10 studies with data from 896 participants were included in this review. Seven articles reported serum creatinine values for each group and 3 of them found significant differences between groups. The random-effects meta-analysis for serum creatinine showed significant lower mean (diff = −52.88 μmol/L [95 % CI -73.65 to −32.11]) in the group of children with pop-off mechanisms, and the random-effects meta-analysis for Nadir serum creatinine showed a marginally significantly lower mean in the group of children with pop-off mechanisms (diff = −12.00 μmol/L [95 % CI -24.04 to 0.04]). The random-effect meta-analysis for Chronic Kidney Disease resulted in a significant risk reduction for the group of children with pop-off mechanisms (odds ratio = 0.48 [95 % CI 0.23 to 0.98]).

Conclusions
Children with PUV and pop-off mechanisms show better renal function and lower risk of Chronic Kidney Disease than those with PUV without pop-off mechanisms suggesting these mechanisms may act as renoprotective mediators. The high heterogeneity between studies in the assessment of renal function and long-term outcomes calls for a cautious interpretation of these findings. Future studies that stratify by different types of pop-off mechanisms and use standardized metrics, such as Nadir creatinine, are needed.

Introduction

Posterior urethral valves (PUV) constitute a very infrequent malformation of the urinary tract that results from an abnormal fusion between the mesonephric duct and the urogenital sinus. PUV represents a lower urinary tract obstruction, which leads to a high-pressure nephrourological pathway. This is associated with bladder disorders such as trabeculation, low bladder capacity and low compliance, secondary vesicoureteral reflux, early and severe nephropathy, and even end-stage Chronic Kidney Disease. In patients with high-pressure nephrourological pathway renal function, measured with serum creatine levels, represent the major prognostic determinant in terms of morbidity and mortality [1].

Part of the renal damage that occurs in these patients happens prenatally. Although intrauterine treatment is an expanding and promising therapeutic field, indications are currently limited, given the high number of complications and the limited therapeutic success rate [2].

Previous studies tried to identify postnatal factors associated with the renal function evolution of patients with PUV. These studies

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include from the evaluation of different markers of renal function during the first year of life to the comparison between different surgical approaches (early urinary diversion and delayed valve ablation vs. early valve ablation, circumcision vs. expectant management, prophylactic antibiotherapy vs. no antibiotherapy) [3—6]. Although previous evidence contributed to a better understanding of the prognosis of this pathology and contributed to reducing its morbidity and mortality, children with PUV still present a high risk of Chronic Kidney Disease (up to 20—50% according to the series) [1,7].

Pop-off mechanisms as described by Rittenberg et al. in 1988 [8] are potential pressure-relieving mechanisms in PUV patients. These mechanisms, usually present from the prenatal period, include urachal persistence, urinary extravasation (urinomas), bladder diverticula, and unilateral high-grade vesicoureteral reflux, including VURD syndrome (posterior urethral valves, unilateral vesicoureteral reflux, and renal dysplasia). It is hypothesized that a pressure decrease in the nephrourological pathway could act as a protective mechanism for renal function in these patients. To date, multiple studies evaluated the potential effect of these mechanisms on the prognosis of patients with PUV, but those studies are heterogeneous and have small sample sizes. This systematic review aimed to synthesize the existing evidence regarding the protective role of pop-off mechanisms on renal function in children with PUV.

Methods

Literature search and selection

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidance. We specifically designed and implemented a review protocol that was registered in the international prospective register of systematic reviews (PROSPERO ID CRD42022370739).

Eligible studies were identified by searching the main existing medical bibliography databases (PubMed, Medline, Scopus, Web of Science, Cochrane Library). Search terms used for medical subject headings and keywords were ("protection" OR "protective" OR "renoprotective" OR "kidney function" OR "renal function" OR "chronic kidney disease" OR "renal failure") AND ("posterior urethral valve" OR "posterior urethral valves" OR "PUV") AND ("pop-off" OR "VURD" OR "VUR" OR "vesicoureteral reflux" OR "renal dysplasia" OR "urinary ascites" OR "urinoma" OR "bladder diverticulum" OR "urinary extravasation" OR "bladder diverticula" OR "megaureter") (supplementary file 1). The search was last executed on 26.01.2023.

The inclusion criteria for this review were: prospective or retrospective original clinical studies evaluating the role of one or more pop-off mechanisms in renal function in pediatric patients diagnosed with PUV. The exclusion criteria for this review were: duplicate or overlapping studies, reviews, systematic reviews, consensus guidelines, case reports or small case series (<10 patients), languages other than English or Spanish, studies with no population of interest, studies with no surgical intervention, studies conducted in adult populations and studies without comparator (control group).

The selection of articles was made by JAM, BPR, and MRJ. Disagreements were resolved through confrontation.

Quality assessment

An analysis of the selected articles according to the Newcastle Ottawa Scale (NOS) standards was conducted to evaluate their methodological quality and to assess the risk of bias. Three reviewers (JAM, BPR, MRJ) independently evaluated the methodological quality and the risk of bias of the selected articles.

Data extract and synthesis

Three reviewers (JAM, BPR, MRJ) independently extracted the relevant data from the selected articles following a standardized procedure. Extracted data included author, year of publication, country where the study was conducted, type of study (prospective or retrospective), study population (sample size, age range), pop-off group and control group definitions, mean and standard deviation (or median and interquartile range) for serum creatinine and Nadir creatinine values in each group, significant events in each group and p-value for between-groups comparison. There were no disagreements or conflicts between the reviewers after collating the extracted data. A review of the metrics used in each of the studies was carried out, and a standardization of units (conversion from mg/dL to μmol/L) was performed for the analysis.

Meta-analysis

Medians and interquartile ranges of serum creatinine and Nadir creatinine were transformed to means and standard deviations following a standard procedure [9]. D'oro et al. [10] provided data not shown in their work after contacting the corresponding author. Five random-effects meta-analysis were performed: 1) all the works that provided serum creatinine levels, 2) all the works that provided serum creatinine levels after excluding Wells et al., 3) all the works that provided serum creatinine levels but including only baseline determinations reported by Heikkilä et al. and Wells et al., 4) all the works that provided serum creatinine levels but including only follow-up determination reported by Heikkilä et al. and Wells et al. and 5) all the works that provided Nadir serum creatinine values.

The decision to exclude the study by Wells et al. in the meta-analysis 2 was based on the fact that the reported initial Creatinine (named in that study Initial Nadir Creatinine) was determined after the decompression of patients' urinary tract and therefore it probably does not represent the lowest creatinine value during the first year of life, which is the definition of Nadir creatinine in the rest of the included studies. The conduct of different meta-analyses (meta-analyses 3 and 4) was based on the idea that baseline and follow-up values for creatinine (as reported by Heikkilä et al. and Wells et al.) are conceptually different and therefore, to avoid a potential bias, they should be separate.

The results were presented in 5 forest plots. A random-effect meta-analysis was performed for the risk of Chronic Kidney Disease. A graphical representation of this analysis

was made in a separate forest plot. Between-study heterogeneity was assessed using Tau2 and I^2 statistics.

Results

The research resulted in 588 articles. 239 duplicates were removed. Among the remaining 349 articles, we excluded 339 following the inclusion and exclusion criteria, resulting in the 10 studies included in this review (Fig. 1). This systematic review includes data from 896 participants aged between 0 and 21 years old.

Pop-off mechanisms as a protective renal factor in posterior urethral valves

The data extracted from the selected 10 studies [8,10—18] is summarized in Table 1. All studies were carried out between 1988 and 2022. Two were from the United States [8,10], 1 from Finland [12], 1 from the United Kingdom [16], 1 from France [18], 1 from Norway [15], 1 from Canada [14], 1 from Spain [17], 1 from Brazil [11], and 1 from Egypt [13]. One study was prospective [11] and the other 9 were retrospective [8,10,12—18]. All the studies involved only pediatric populations.

The NOS score was "good" in 8 of the 10 studies [10—13,15—18] and "poor" in the remaining 2 [8,14]. The NOS score results obtained by each study are shown in Fig. 2.

The definitions of both "case" and "control" were consistent throughout all the included studies. Cases were defined as patients with PUV and at least one pop-off mechanism (bladder diverticula, patent urachus, unilateral high-grade vesicoureteral reflux, VURD syndrome, urinoma), while controls were defined as patients with PUV in which the presence of any pop-off mechanisms had not been diagnosed [8,10—18].

The timing to assess patients' renal function was inconsistent throughout the included studies. Two studies

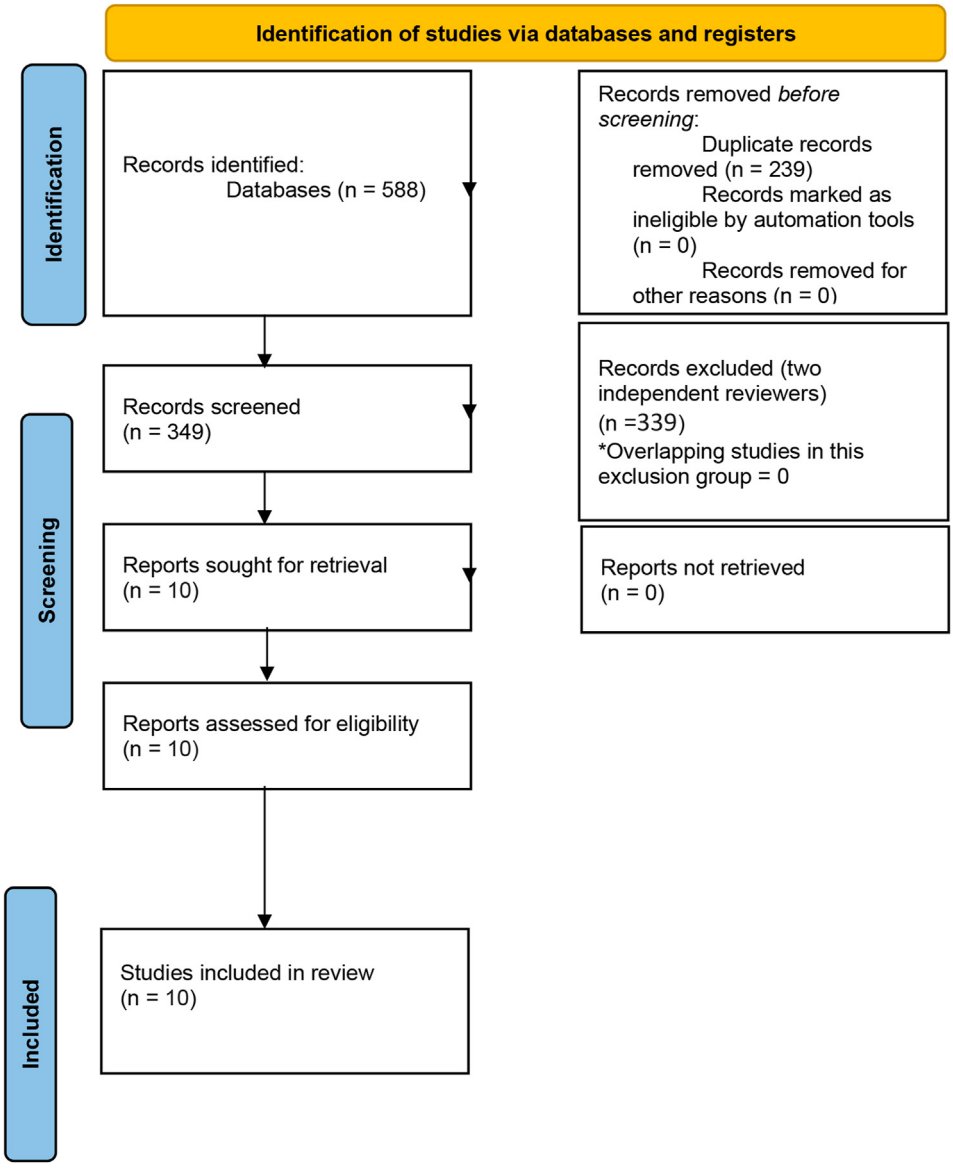


Fig. 1 Flow diagram of the search and selection process.

Table 1 Summary of the publications included in this systematic review.

Authors (year)	Study design	Age (Range)	Sex M/F	Total *N*	*N* in 'Pop-off' group	*N* in 'non Pop-off' group	Serum Cr in 'Pop-off' group	Serum Cr in 'non Pop-off' group	Significant events/renal function outcomes in 'Pop-off' group	Significant events/renal function outcomes in 'non Pop-off' group	Follow-up time	*p* value for serum Cr comparison between groups
Rittenberg et al. (1988) [8]	Retrospective cohort	2.5-8y	71/0	71	Total: 20 (VURD: 9 Urinary ascites: 3 Perinephric urinoma: 3 1 to 3 bladder diverticula: 5)	51	Preoperative Cr:[h] 88.4 (44.2—238.68)[a] μmol/L (114.92 ± 52.04)[e] μmol/L Follow up Cr:[h] Cr > 88.4 μmol/L: 1 (5 %) Cr < 88.4 μmol/L: 19 (95 %)	Follow up Cr: Cr > 88.4 μmol/L: 20 (40 %)[h] Cr: <88.4 μmol/L: 31 (60 %)[h]	RRT and/or KT: 0/20 (0 %)	RRT and/or KT: 7/51 (13.7 %)	Pop-off group: (1—14) [a]y Non pop-off group: (0.5—15)[a]y	**p < 0.01**
Oliveira et al. (2002) [11]	Prospective cohort	—	—	22	8 (Unilateral VUR:8)	Total: 14 (No VUR: 4 Bilateral VUR: 10)	—	—	Unilateral VUR: CRF[k]: 2/8 (25 %)	Bilateral VUR: CRF[k]: 9/14 (64.3 %)	76 (8—148)[a]m	—
Heikkilä et al. (2009) [12]	Retrospective cohort	0-25y (at diagnosis)	—	197	Total: 54 (Unilateral VUR: 54)	Total: 143 (No VUR: 70 Bilateral VUR: 73)	At diagnosis: Unilateral VUR: Cr 97 (21—433)[a] μmol/L (162 ± 90.64)[e] μmol/L 5-7y post-surgery: Unilateral VUR: Cr 60 (29—583)[a] μmol/L (183 ± 121.9)[e] μmol/L	At diagnosis: No VUR: Cr 66 (19—374)[a] μmol/L (131.25 ± 74.89)[e] μmol/L Bilateral VUR: Cr 130 (14—593)[a] μmol/L (216.75 ± 121.37)[e] μmol/L 5-7y post-surgery: No VUR: Cr 54 (34—477)[a] μmol/L (154.75 ± 93.46)[e] μmol/L Bilateral VUR: Cr 66 (43—592)[a] μmol/L (191.75 ± 115.08)[e] μmol/L	—	—	8y	—
Wells et al. (2010) [16]	Retrospective cohort	—	89/0	89	9 (urinoma:9)	80	Initial NCr:[i] 31 (18—44)[a] μmol/L (31 ± 8.70)[e] μmol/L Follow-up Cr: 44 (25—77)[a] μmol/L (47.5 ± 17.40)[e] μmol/L	Initial NCr:[i] 45 (20—574)[a] μmol/L (171 ± 114.52)[e] μmol/L Follow-up Cr: 61 (29—1227) [a] μmol/L (344.5 ± 247.65)[e] μmol/L	ESRF/KT: 0/9 (0 %)	ESRF/KT: 9/80 (11.25 %)	Urinoma: 5.1 (2.2—17.3)[a]y No urinoma: 5.9 (1.8—19.7)[a]y	Initial: **P < 0.01**[f] Follow up: **P < 0.05**

Sarhan et al. (2011) [13]	Retrospective cohort	0-15y	–	120	Unilateral VUR: 33	Total: 87 (No VUR:63 Bilateral VUR: 24)	–	–	Unilateral VUR CRF[i]: 12/33 (36.4 %)	No VUR CRF[i]: 22/63 Bilateral VUR CRF[i]: 10/24 Total: 32/87 (36.8 %)	3.6 (2–16)[a]y	NS
Hoag et al. (2013) [14]	Retrospective cohort	–	89/0	89	23 (VURD: 23)	66	95 (30–451)[a] μmol/L[f] (167.75 ± 109.14)[e] μmol/L NCr: 88 μmol/L	108 (20–570)[a] μmol/L[f] (201 ± 117.11)[e] μmol/L NCr: 82 μmol/L	–	–	–	p = 0.07
Lundar et al. (2019) [15]	Retrospective cohort	–	60/0	60	12 (prenatal extravasation of urine: 12)	48	NCr: 21 (11–33)[a] μmol/L[f] (21.5 ± 6.73)[e] μmol/L	NCr: 23 (14–199)[a] μmol/L[f] (64.75 ± 41.52)[e] μmol/L	CKD II-V (including KT) 1/12 (8.3 %)	CKD II-V (including KT) 20/48 (41.7 %)	Non pop-off group: 5.3 (0.2–16.9[a])y Pop-off group: 4.1(0.6–13.1) [a]y	**p=0.025**
D'oro et al. (2020) [10]	Retrospective cohort	1-12.2y	41/0	41	28 (VURD: 13 VURD/VUR: 7 VUR:5 Urinoma:3 Patent Urachus: 2 Urinary Ascites:1)	13	NCr: 0.35 (0.3–0.4)[b] mg/dL (as provided by author) 30.95 (26.5–35.4)[b] μmol/L[h] (30.95 ± 6.95) μmol/L[3b]	Ncr: 0.33 (0.25–0.4)[b] mg/dL (as provided by author) 29.18 (22.1–35.4)[b] μmol/L[h] (28.9 ± 11.05) μmol/L[3b]	–	Unsafe voiding pressures on UD	5.9 (1–12.2)[j], [a]y	p = 0.92
Massaguer et al. (2022) [17]	Retrospective cohort	5.5–10.9y[g]	–	70	14 (unilateral VUR: 7 Diverticula: 2 Ascites:2 Unilateral VUR + diverticula: 2 Unilateral VUR + urinoma: 1)	56	NCr: 0.37 (0.35 –0.4)[b] mg/dL Ncr: 32.71 (30.94 –35.36)[b] μmol/L (33 ± 3.64)[3b] μmol/L	NCr: 0.4 (0.35–0.49)[b] mg/dL Ncr: 35.36 (30.94 –43.32)[b] μmol/L (36.54 ± 9.42)[3b] μmol/L	CKD 0/14 (0 %) RRT 0/14 (0 %)	CKD 15/56 (27 %) RRT 5/56 (9 %)	Non pop-off group: 7.4 (4.0 –10.1)[j,a]y Pop off group: 7.6 (4.0–10.1)[j,a]y	p = 0.17
Delefortrie et al. (2022) [18]	Retrospective Cohort	–	137/0	137	39 (VURD:19 (Urinoma:16 (Bladder diverticula:9)	98	NCr: (35.7 ± 12.2)[c] μmol/L	NCr: (44.5 ± 29.9)[c] μmol/L	CRF 14/32 (43.7 %)	CRF 34/70 (48.6 %)	8.3 (6.9–12.6)[b] y	p = 0.31

VUR: Vesicoureteral reflux; **NCr**: Nadir serum creatinine, **Cr**: Serum creatinine; **FUTI**: Febrile urinary tract infection; **CKD**: Chronic Kidney Disease; **RF**: Renal failure; **RRT**: Renal replacement therapy; **KT**: Kidney transplant; **UD**: Urodynamic study **CRF**: Chronic renal failure **ESRF**: End-stage renal failure.

[a] Median (range).
[b] Median (interquartile range).
[c] (Mean ± standard deviation).
[3b] (Mean ± standard deviation) estimated with median (Interquartile range).
[e] (Mean ± standard deviation) estimated with median (range).
[f] At birth.
[g] Current age at the time when the study was conducted.
[h] Original units reported as mg/dL.
[i] Defined as the minimum value to which Cr fell after decompression of the urinary tract and recovery from postobstructive diuresis).
[j] Age of the patient at the last follow-up.
[k] Defined as GRF lower than normal levels for age.
[l] Chronic renal failure was defined as the stage at which eGFR was 59 ml per minute/1.73 m^2 or less according to National Kidney Foundation guidelines.

	Selection bias assessment				Comparability	Outcome				
Study ID	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability	Assessment of the outcome	Was follow-up long enough for the outcomes to occur?	Adequacy of follow-up	Total 9/9	Conversion to AHRQ
Rittenberg, 1988	☆	☆	☆	☆	0	☆	☆	☆	7/9	Poor
Oliveira, 2002	☆	☆	☆	☆	☆	0	☆	☆	7/9	Good
Heikkilä, 2009	☆	☆	☆	☆	☆	☆	☆	0	7/9	Good
Wells, 2010	☆	☆	☆	☆	☆	☆	☆	☆	8/9	Good
Sarhan 2011	☆	☆	☆	☆	☆	☆	0	☆	7/9	Good
Hoag, 2013	☆	☆	☆	☆	0	0	☆	☆	6/9	Poor
Lundar, 2019	☆	☆	☆	☆	☆	☆	☆	☆	8/9	Good
D'oro 2022	☆	☆	☆	☆	☆	0	☆	☆	7/9	Good
Massaguer, 2022	☆	☆	☆	☆	☆	☆	☆	☆	8/9	Good
Delefortrie, 2022	☆	☆	☆	☆	☆	☆	☆	☆	8/9	Good

Fig. 2 Bias assessment of the included studies in the review (Newcastle—Ottawa scale).

reported serum creatinine values at birth [14,15], 1 study reported serum creatinine values at diagnosis [12], 1 study reported preoperative serum creatinine values [8], and 5 studies reported Nadir creatinine values (defined as the lowest creatinine value during the first year after diagnosis) [10,14,15,17,18]. Two studies did not provide any serum creatinine value [11,13]. One study provided "Initial Nadir Creatinine", defined as the minimum value to which serum creatinine fell after decompression of the urinary tract and recovery from post obstructive diuresis [16]. The follow-up time ranged from 0.5 to 19.7 years. Regarding serum creatinine values at follow-up, 1 study reported stratified values at different periods [12], 1 study reported "current creatinine" as follow-up creatinine [16] and 1 study did not specify the follow-up time [8].

Serum creatinine values were presented as median (range) [8,12,14—16], median (interquartile range) [10] or mean (standard deviation) [18]. Six studies expressed serum creatinine values in μmol/L [8,12,14—16,18] and 2 studies in mg/dL [10,17].

Three articles reported significant differences in serum creatinine values between groups [8,15,16], 5 articles reported non-significant differences [10,13,14,17,18], and 2 articles did not report a p-value for the between-groups comparison [11,12].

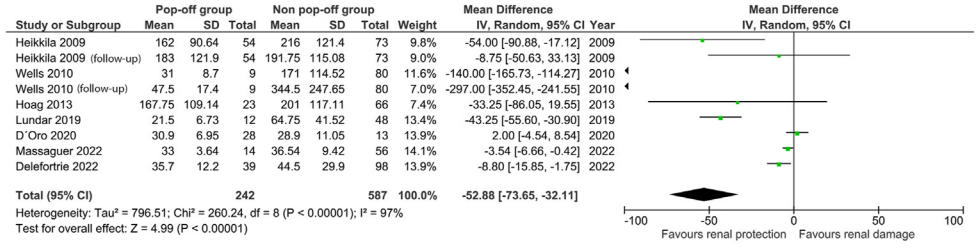
Seven studies reported data regarding the incidence of Chronic Kidney Disease [8,11,13,15—18], but the definition of Chronic Kidney Disease was inconsistent. One article defined Chronic Kidney Disease as a glomerular filtration rate (GFR) below the age-specific level of reference [11], while others followed the National Kidney Foundation guidelines and defined Chronic Kidney Disease as GFR $<$59 ml per minute/1.73 m^2 [13]. Data was presented as relative risk for Chronic Kidney Disease [11], the number of patients that developed Chronic Kidney Disease by group [11,13,15—18], the proportion of patients that required kidney transplantation [8,15,16] or renal replacement therapy (RRT) [8,17].

Regarding Chronic Kidney Disease, Oliveira et al. [11] reported 9 patients (64.3 %) in the non-pop-off group and 2 (25 %) in the pop-off group, Sarhan et al. [13], 32 (36.8 %) and 12 (36.4 %) cases in each group respectively, Lundar et al. [15], 15 (31.3 %) and 1 (8.3 %), Massaguer et al. [17], 15 (27 %) and 0, and Delefortrie et al. [18], 34 (48.6 %) and 14 (43.7 %).

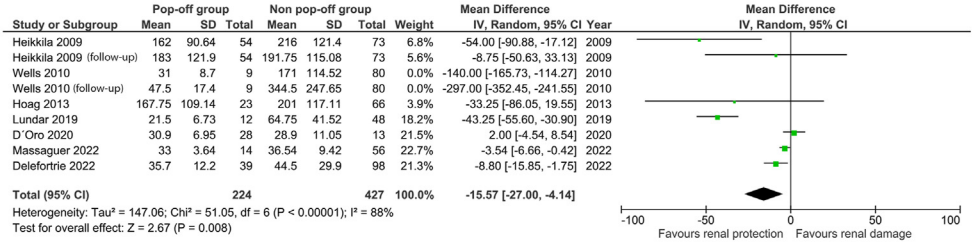
Rittenberg et al. [8] reported 7 patients (13.7 %) who required renal dialysis and/or transplantation in the non-pop-off group while 0 in the pop-off group. Wells et al. reported 9 patients (11.25 %) in end-stage Chronic Kidney Disease and/or transplantation in the non-pop-off group while 0 in the pop-off group. Lundar et al. [15] reported 5 patients (10.4 %) in the non-pop-off group and 0 patients in the pop-off group which required renal transplantation. Massaguer et al. [17] reported 5 (9 %) patients in the non-pop-off group and 0 in the pop-off group requiring RRT.

Serum creatinine values in children with PUV with or without pop-off mechanisms: meta-analysis

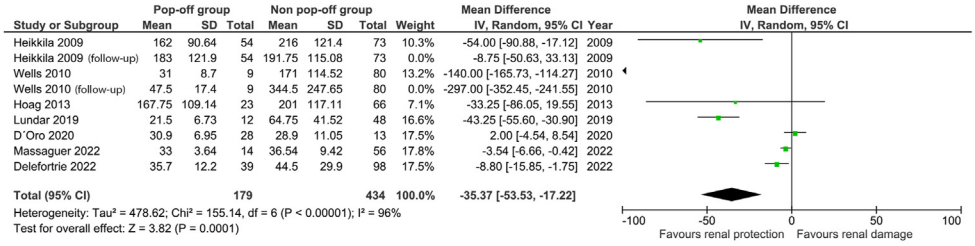
Five random-effects meta-analyses were performed (Fig. 3). In all the analyses the overall mean difference was favorable to the group of children with PUV and pop-off mechanism. The first one included all the works that provided serum creatinine values [10,12,14—18] and resulted in a significant mean difference of −52.88 μmol/L [95 % CI -73.65 to −32.11] ($p < 0.00001$) with a Chi^2 of 260.24 and a I^2 of 97 %. The second one included all the works that provided serum creatinine values after excluding the study by Wells et al. [10,12,14,15,17,18] and showed a significant mean difference of −15.57 μmol/L [95 % CI -27.00 to −4.14] ($p = 0.008$) with a Chi^2 of 51.05 and a I^2 of 88 %. The third one included all the works that provided serum creatinine values, but only considered baseline determinations of the studies by Heikkilä et al. and Wells et al. [10,12,14—18]. This meta-analysis showed a significant mean difference of −35.37 μmol/L [95 % CI -53.53 to −17.22] ($p = 0.00001$) with a Chi^2 of 155.14 and a I^2 of 96 %. The fourth meta-analysis included all the works that provided serum creatinine values, but only considered follow-up determinations of the studies by Heikkilä et al. and Wells et al. [10,12,14—18]. This analysis showed a significant mean difference of −34.66 μmol/L [95 % CI -53.49 to −15.82] ($p = 0.0003$) with a Chi^2 of 150.54 and a I^2 of 96 %. The last meta-analysis included all the works that provided Nadir serum creatinine values [10,15,17,18] and resulted in a



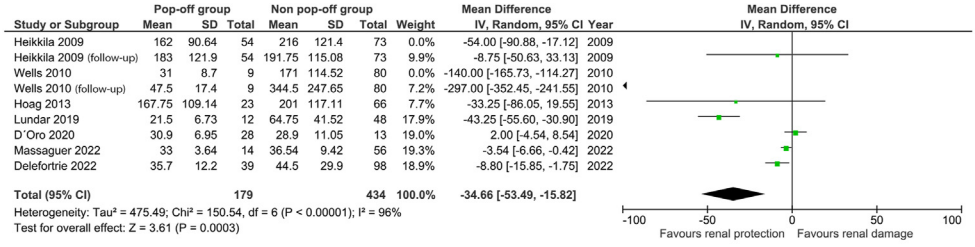
A. Analysis including all works (Wells et al and Heikkila: diagnosis and follow-up measures included)



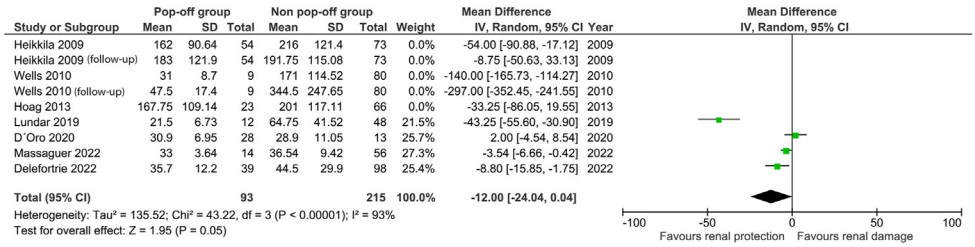
B. Analysis including all works (except from Wells et al)



C. Analysis including all works (Wells et al and Heikkilä et al: only diagnosis Cr included)



D. Analysis including all works (Wells et al and Heikkilä et al: only follow-up Cr included)



E. Analysis including all Nadir Cr works

Fig. 3 Forest plot of the 5 random-effects meta-analyses for mean serum creatinine values (pop-off vs. non-pop-off groups).

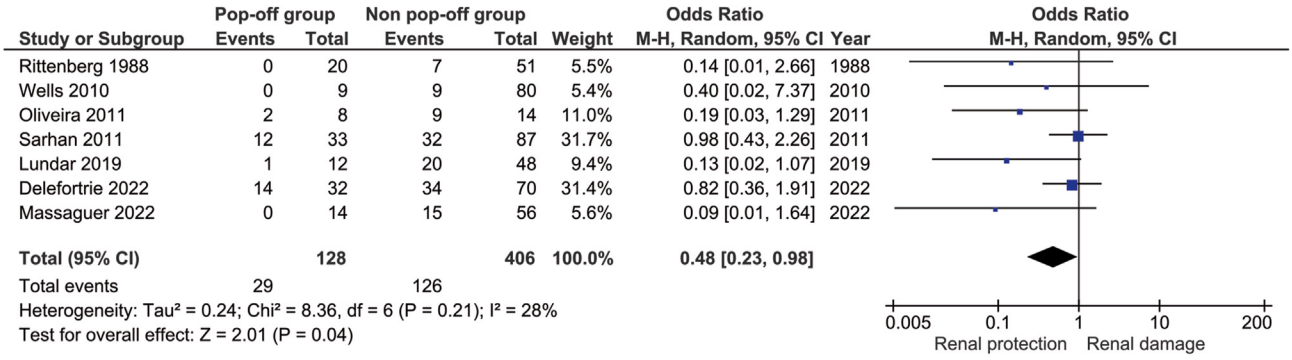


Fig. 4 Forest plot of the random-effects meta-analysis for Chronic Kidney Disease (pop-off vs. non pop-off groups).

marginally significant mean difference of −12.00 μmol/L [95 % CI -24.04 to 0.04] (p = 0.05) with a Chi^2 of 43.22 and a I^2 of 93 %.

Chronic kidney disease in children with PUV with or without pop-off mechanisms: meta-analysis

We performed a random-effect meta-analysis for Chronic Kidney Disease including patients who had been diagnosed with Chronic Kidney Disease, those who required renal replacement therapy, and those who underwent kidney transplantation. We obtained a relative risk reduction of 52 % in the group of children with PUV and pop-off mechanisms (OR = 0.48 [95 % CI 0.23 to 0.98]) (p = 0.04) with a Chi^2 of 8.36 and a I^2 of 28 % (Fig. 4).

Discussion

In this systematic review and meta-analysis, we synthesized the existing evidence regarding the effect of pop-off mechanisms in children with PUV and we found that these mechanisms may act as renoprotective mediums. This finding is supported by the results of 5 meta-analyses that resulted in significantly lower serum creatine levels (and therefore better renal function) in the group of children with PUV and pop-off mechanisms and a meta-analysis that showed a significant relative risk reduction for Chronic Kidney Disease associated with them.

These results are of great significance for several reasons: 1) They justify the stratification of patients diagnosed with PUV into patients at higher and lower risk of Chronic Kidney Disease based on the presence or absence of these mechanisms. 2) They lay the groundwork and allow to orient new lines of work in this field: for example, prospective studies in patients with PUV that systematically evaluate objective parameters such as Nadir Creatinine or renal outcome by subtype of pop-off mechanism.

From a biological point of view and in terms of pathophysiological plausibility, stating that pop-off mechanisms are renoprotective is logical: the release of pressure through an escape pathway decreases the damage to the system. Metaphorically, they would act like the exhaust valve of a boiler: when the pressure exceeds an acceptable limit, the valve pops and the pressure escapes. Nevertheless, and although this reflection is reasonable, this work provides an extensive and systematic review of this fact with a quantitative analysis of the existing data in the scientific literature which allows us to confirm the hypothesis.

We acknowledge the high heterogeneity between studies may have hampered our results. This heterogeneity may be attributed to multiple factors, including the variability in serum creatinine values, which may be explained by the timing of the determinations and differences in the processing, among others. for example, some authors reported serum creatinine level at birth, which is probably affected by the transplacental passage. We identified the work by Wells et al. [16] as a potential source of heterogeneity because they reported "Initial Nadir creatinine" using a definition that we did not find in any other study. However, the meta-analyses excluding data reported by Wells et al. still showed high heterogeneity, suggesting there might be other sources of heterogeneity that we did not manage to identify. In addition, although valid mean and standard deviation (needed for the meta-analysis) can be estimated from the median and interquartile range, many authors only reported the median and range, which is an unreliable measure of dispersion. We consider that the presence of outliers might have artificially increased the standard deviation we calculated for the meta-analyses, making it more difficult to obtain statistically significant results. Along with this, the presence of wide confidence intervals in some of the included studies may have also hampered our analyses similarly. Nevertheless, when studies with a wide confidence interval (Heikkila et al. and Wells et al.) were eliminated from the meta-analysis, the magnitude of the association decreased but did not lose statistical significance. Lastly, the lack of standardization in the definitions of each pop-off mechanism constitutes a limitation for this work.

On the other hand, the meta-analysis for Chronic Kidney Disease showed very low heterogeneity, probably due to a relatively standardized definition of the case.

A relevant aspect to comment on is that, although several pop-off mechanisms are universally accepted as such and therefore homogeneously reported, there are some mechanisms whose pop-off effect is dubious (i.e.

unilateral high-grade vesicoureteral reflux) hence their prevalence may be underestimated (which is why we chose to perform a random-effects meta-analysis). Although Table 1 describes the type of pop-off mechanism observed in each study, we could not perform a stratified analysis due to the lack of individual data. Nevertheless, we cannot assume that all pop-off mechanisms will be equally protective, and consequently, stratified analysis by the type of pop-off mechanism, while considering the age of the patient, will need to be addressed in future studies.

The inclusion of the two types of meta-analysis (mean difference in serum creatinine levels and risk of Chronic Kidney Disease) represents one of the main strengths of this work since the results obtained in both analyses are consistent and support the potential mediating effect of the pop-off mechanism in the protection of the kidney of children with PUV. Last, but not least, we followed a rigorous methodology, with a precise adherence to the PRISMA guidelines and the Newcastle Ottawa scale [19,20].

In conclusion, pop-off mechanisms may be a renoprotective mediator in children with PUV. The high between-study heterogeneity, the variability in reporting metrics and outcomes as well as the absence of stratified analyses by the type of mechanism justify the need for further prospective studies.

Conflict of interest

The authors declare that they have no conflict of interest.

CRediT authorship contribution statement

JAM: Conceptualization and study design; literature search and selection, data curation and extraction, formal analysis; investigation; methodology; project administration; resources; validation; visualization; writing — original draft; writing — review and editing.

NMC: Formal analysis; methodology; validation; visualization; writing — original draft; writing — review and editing.

BPR, MRJ: literature search and selection, data curation and extraction, writing — original draft; writing — review and editing.

OEB: visualization; writing — review and editing.

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Ethical approval

This article did not involve work with human patients or animal experimentation and therefore no ethics committee approval was requested.

Statement of availability of the data used during the systematic review

The data used to carry out this systematic review is available upon request from the reviewers.

Conflict of interest

The authors declare that they have no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpurol.2023.10.003.