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

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Systematic Review

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Abstract

Background

Pop-off mechanisms are potential pressure-relieving mediators in patients diagnosed with posterior urethral valves (PUV). These mechanisms include, among others, urachal persistence, urinomas, bladder diverticula and unilateral high-grade vesicoureteral reflux. The aim of this systematic review was 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 medical bibliography. Three independent reviewers selected the relevant articles based on the previously defined inclusion and exclusion criteria. Methodological quality of the selected article was rated using the Newcastle Ottawa Scale index. Data extraction was performed by three independent reviewers. We used random meta-analyses to compare different outcomes (serum creatine, Nadir serum creatinine, and renal failure) between children with PUV and pop-off mechanisms and those with PUV but without pop-off mechanisms.

Results

10 studies with data from 896 participants were included in this review. The age of the participants ranged from 0 to 25 years. 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 significant 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 renal failure resulted in a significant risk reduction on 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 renal failure than those with PUV but without pop-off mechanisms suggesting these mechanisms may act as renoprotective mediums. The high heterogeneity between studies in the assessment of renal function and long-term outcomes compel to interpret these findings with caution. Future studies that stratify by the 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. In practice, PUV represent a urinary tract obstruction, which leads into a high-pressure nephrourological pathway. This is associated with bladder disorders such as trabeculation, low bladder capacity and low compliance, vesicoureteral reflux, early and severe nephropathy, and even end-stage renal failure. In patients with high-pressure nephrourological pathway renal function, measured by serum creatine levels, represent the major prognostic determinant [1].

The incidence of PUV is 1 per 5,000–8,000 male live births, depending on the series. Part of the renal damage that occurs in these patients happens prenatally. However, although the advances in prenatal diagnosis made it possible to establish early diagnostic suspicion, intrauterine treatment is still underdeveloped and the results are inconsistent [2].

A recent bibliometric study showed that long-term prognosis of patients with PUV is one of the fields of greatest scientific interest nowadays [3]. Previous studies tried to identify postnatal factors associated with the renal function evolution of patients with PUV. These studies 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) [4–6]. Although previous evidence contributed to a better understanding of the prognosis of this pathology and contributed to reduce its morbidity and mortality, children with PUV still present a high risk of renal failure (up to 20–50% according to the series) [1,7] noting that there is still room for improvement in the management of these patients.

Pop-off mechanisms as described by Rittenberg 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). 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 little sample sizes. The aim of this systematic review was 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 in the main existing medical bibliography databases (PubMed, Medline OVID, 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 renal 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”). The search was last executed on 26.01.2023.

Inclusion and exclusion criteria are shown in Supplementary file 1. The selection of articles was made by JAM, BPR and MRJ. Disagreement was resolved by confrontation.

**Quality Assessment**

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

**Data Extract And Synthesis**

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 and sex distribution), 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 showed 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 that by 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 results were presented in 5 forest plots. Also, a random-effect meta-analysis was performed for the risk of chronic renal failure. A graphical representation of this analysis was made in a separate forest plot. Between study heterogeneity was assessed using the Tau2 and I² 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 to 25 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 Unites 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 score in the NOS was “good” in 8 of the 10 studies [10,11,12,13,15–18] and “poor” in the remaining 2 [8, 14]. The result each study obtained in the NOS is shown in Fig. 2.

The definition of both “case” and “control” was consistent through 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 through the included studies. Two studies reported serum creatinine values at birth [14,15], 1 study reported serum creatinine values of 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 the diagnosis) [10,14,15,17,18]. Two studies did not provide any creatinine serum 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 postobstructive 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 time 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 renal failure (RF) [8,11,13,15–18], but the definition of renal failure was inconsistent. One article defined renal failure as a glomerular filtration rate (GFR) below the age-specific level of reference [11], while others defined renal failure as GFR < 59 ml per minute/1.73 m² according to the National Kidney Foundation guidelines [13]. Data were presented as relative risk for chronic renal failure [11], the number of patients that developed chronic renal failure 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 renal failure, 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%) which 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 renal failure 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 which required RRT.

Serum Creatinine Values In Children With PUV With Or Without Pop-off Mechanisms: Meta-analysis

Five random-effects meta-analysis 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 < 0.0001) with a Chi² of 260.24 and a I² 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 = 0.007) with a Chi² of 51.05 and a I² 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 = 0.0001) with a Chi² of 155.14 and a I² 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 Chi² of 150.54 and a I² of 96%. The last meta-analysis included all the works that provided Nadir serum creatinine values [10,15,17,18] and resulted in a marginally significant mean difference of -12.00 μmol/L [95% CI -24.04,0.04] (p = 0.05) with a Chi² of 43.22 and a I² of 93%.

Chronic renal failure in children with PUV with or without pop-off mechanisms: meta-analysis.

We performed a random-effect meta-analysis for chronic renal failure including patients that had been diagnosed with chronic renal failure, those that required renal replacement therapy, and those that 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 Chi² of 8.36 and a I² 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 found that these mechanisms may act as renoprotective mediums. This finding is supported by the results of 5 meta-analyses that resulted in significant lower serum creatinine levels (and therefore better renal function) in the group of children with PUV and pop-off mechanisms and the meta-analysis that showed a significant relative risk reduction for renal failure associated with them. 

These results are of great significance for several reasons: 1) They justify stratification of patients diagnosed with PUV into patients at higher and lower risk of renal failure based on the presence or absence of these mechanisms. This, in turn, can lead to the creation of specific follow-up algorithms for each subgroup, being narrower in the case of patients without pop-off 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, that pop-off mechanisms are renoprotective is logical: the release of pressure through an escape pathway decreases the damage to the system. In metaphorical terms, 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 hampered our results. This heterogeneity may be attributable to multiple factors, including the variability in serum creatinine values, which may be explain 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 artifactual by the transplacental passage. We identified the work by Wells et al. [16] as a potential source of heterogeneity based on the fact that 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 reach to identify. In addition, although valid mean and standard deviation (needed for the meta-analysis) can be estimated from median and interquartile range, many authors only reported 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. On the other hand, the meta-analysis for chronic renal failure showed very low heterogeneity, probably due to a relatively standard definition of the case.

A relevant aspect to comment on is that, although several pop-off mechanism 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) and 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 performed a stratified analysis due to the lack of data in the individual. 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 and sex 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 renal failure) 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, and the absence of stratified analyses by the type of mechanism justify the need for further prospective studies.

Declarations

ACKNOWLEDGEMENTS: No acknowledgements to report.

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; investigation; methodology; project administration; resources; 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.

FINANCIAL STATEMENT/FUNDING:

This review did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. None of the authors have external funding to declare.

CONFLICTS OF INTEREST:

The authors declare that they have no conflict of interest.

ETHICAL APPROVAL:

This study did not involve the participation of human or animal subjects, and therefore was exempt from formal assessment by the ethics committee for clinical research of our center.

CONFLICT OF INTEREST:

No financial or non-financial benefits have been received or will be received from any party related directly or indirectly to the subject of this article.

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.

References


Tables

Table 1. Summary of the publications included in this systematic review.
<table>
<thead>
<tr>
<th>Author</th>
<th>Study design</th>
<th>Age (Range)</th>
<th>Sex M/F</th>
<th>Total N</th>
<th>N in 'Pop off' group</th>
<th>N in 'non-Pop off' group</th>
<th>Serum Cr in 'Pop off' group</th>
<th>Serum Cr in 'non-Pop off' group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rittenberg et al</td>
<td>Retrospective cohort</td>
<td>2.5-8y</td>
<td>71/0</td>
<td>71</td>
<td>Total: 20 (VURD: 9 Urinary ascites: 3 Perinephric urinoma: 3 1 to 3 bladder diverticula: 5)</td>
<td>51 Preoperative Cr: **** 88.4 (44.2-238.68)1 μmol/L (114.92±52.04)4 μmol/L Follow up Cr: **** Cr &gt;88.4 μmol/L: 1 (5%) Cr &lt;88.4 μmol/L: 19 (95%)</td>
<td>Follow up Cr:</td>
<td>CR: &gt;88.4 μmol/L: 20 (40%) **** CR: &lt;88.4 μmol/L: 1 (5%) ****</td>
</tr>
<tr>
<td>Oliveira et al</td>
<td>Prospective cohort</td>
<td>- - 22</td>
<td>8</td>
<td>18</td>
<td>Total: 14 (Unilateral VUR: 8)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Heikkilä et al</td>
<td>Retrospective cohort</td>
<td>0-25y (at diagnosis)</td>
<td>- 197</td>
<td>54 Total: 143 (Unilateral VUR: 54)</td>
<td>At diagnosis: Unilateral VUR: Cr 97 (21-433)1 μmol/L (162±90.64)4 μmol Bilateral VUR: Cr 130 (14-593)1 μmol/L (216.75±121.37)4 μmol 5-7y post-surgery: Unilateral VUR: Cr 60 (29-583)1 μmol/L (183±121.9)4 μmol Bilateral VUR: Cr 66 (43-592)1 μmol/L (191.75±115.08)4 μmol</td>
<td>At diagnosis:</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Wells et al</td>
<td>Retrospective cohort</td>
<td>- 89/0</td>
<td>89</td>
<td>9</td>
<td>80 Initial NCr:***** 45 (20-574)1 μmol/L (171±114.52)4 μmol Follow-up Cr: Initial NCr:***** 31 (18-44)1 μmol/L (31±8.70)4 μmol Follow-up Cr: 44 (25-77)1 μmol/L (47.5±17.40)4 μmol</td>
<td>ESRF/KT</td>
<td>9 (0%)</td>
<td></td>
</tr>
<tr>
<td>Sarhan et al</td>
<td>Retrospective cohort</td>
<td>0-15y</td>
<td>- 120</td>
<td>Unilateral VUR: 33 Total: 87</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Unilateral VUR</td>
</tr>
<tr>
<td>Study</td>
<td>Type of Study</td>
<td>Age/Duration</td>
<td>Studies</td>
<td>NVUR</td>
<td>Bilateral VUR</td>
<td>CRF%^^</td>
<td>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</td>
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<tr>
<td>Lundar et al (2019) [15]</td>
<td>Retrospective cohort</td>
<td>60/0</td>
<td>60</td>
<td>12 (prenatal extravasation of urine: 12)</td>
<td>48</td>
<td>NCr: 21 (11-33) µmol/L* (21.5±6.73) µmol</td>
<td>NCr: 23 (14-199) µmol/L* (64.75±41.52) µmol</td>
<td>CRF II-V (including KT) 1/12 (8.3)</td>
</tr>
<tr>
<td>D’oro et al (2020) [10]</td>
<td>Retrospective cohort</td>
<td>1-12.2y</td>
<td>41/0</td>
<td>41</td>
<td>28 (VURD: 13 VURD/VUR: 7 VUR: 5 Urinoma: 3 Patent Urachus: 2 Urinary Ascites: 1)</td>
<td>13</td>
<td>NCr: 0.35 (0.3-0.4)² mg/dL (as provided by author)</td>
<td>NCr: 0.33 (0.25-0.4)² mg/dL (as provided by author)</td>
</tr>
<tr>
<td>Massaguer et al (2022) [17]</td>
<td>Retrospective cohort</td>
<td>5.5-10.9y ***</td>
<td>-</td>
<td>70</td>
<td>14 (unilateral VUR: 7 Diverticula: 2 Ascites: 2 Unilateral VUR + diverticula: 2 Unilateral VUR+ urinoma: 1)</td>
<td>56</td>
<td>NCr: 0.37 (0.35-0.4)² mg/dL Ncr: 32.71 (30.94-35.36)² µmol/L</td>
<td>NCr: 0.4 (0.35-0.49)² mg/dL Ncr: 35.36 (30.94-43.32)² µmol/L CKD 0/14 (0% RRT 0/14 (0%</td>
</tr>
<tr>
<td>Delefortrie et al (2022) [18]</td>
<td>Retrospective cohort</td>
<td>137/0</td>
<td>137</td>
<td>39 (VURD:19 Urinoma:16 Bladder diverticula:9)</td>
<td>98</td>
<td>NCr: (35.7±12.2)³ µmol/L</td>
<td>NCr: (44.5±29.9)³ µmol/L</td>
<td>CRF 14/32 (43.7%)</td>
</tr>
</tbody>
</table>

**Notes:**
- Median (range) or mean ± standard deviation are provided.
- 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
- NVUR: Number of Vesicoureteral reflux cases.
- Bilateral VUR: Number of bilateral vesicoureteral reflux cases.
- CRF%^^: Chronic renal failure percentage (total number of patients).
- Median (range) or mean ± standard deviation are provided.
- *: At birth; **: Univariate analysis of pop-off mechanism and renal impairment; ***: Current age at the time when the study was conducted.
- Original units reported as mg/dL. 
- ****: Defined as the minimum value to which Cr fell after decompression of the urinary tract and recovery from postobstructive diuresis.
- X: Age of the patient at the last follow-up.
Supplementary Files

Supplementary File 1 is not available with this version

Figures

Figure 1

Flow diagram of the search and selection process.

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Representativeness of the exposed cohort</th>
<th>Selection of the non-exposed cohort</th>
<th>Ascertainment of exposure</th>
<th>Demonstration that outcome of interest was not present at start of study</th>
<th>Comparability</th>
<th>Assessment of the outcome</th>
<th>Was follow-up long enough for the outcomes to occur?</th>
<th>Adequacy of follow-up</th>
<th>Total 9/9</th>
<th>Conversion to AHRQ</th>
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<td>✮</td>
<td>✮</td>
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<td>✮</td>
<td>7/9</td>
<td>Poor</td>
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<td>✮</td>
<td>✮</td>
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<td>✮</td>
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<td>✮</td>
<td>7/9</td>
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<td>Heikkinen, 2009</td>
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<td>✮</td>
<td>✮</td>
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<td>✮</td>
<td>7/9</td>
<td>Good</td>
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Figure 2

Bias assessment of the included studies in the review (Newcastle-Ottawa scale).

Figure 3

Forest plot of the 5 random-effects meta-analyses for mean serum creatinine values (pop-off vs. non-pop-off groups).
Figure 4

Forest plot of the random-effects meta-analysis for chronic renal failure (pop-off vs. non pop-off groups).

Random-effects meta-analysis for chronic renal failure/renal replacement therapy/kidney transplantation