REVIEW

What are the Effective Factors in Spontaneous Resolution Rate of Primary Vesicoureteral Reflux: A Meta-Analysis and Systematic Review

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Purpose: This meta-analysis aimed to predict the rate of spontaneous resolution and identify influencing factors among pediatric patients with primary vesicoureteral reflux (VUR). The primary objective was to construct a nomogram to facilitate clinical decision-making in the treatment of primary VUR by assessing the rate of spontaneous resolution and its determinants.

Materials and Methods: A systematic search was conducted up to September 2023, encompassing databases such as PubMed, Web of Science, Scopus, and the reference lists of relevant studies. Inclusion criteria comprised 33 studies with a total of 8540 pediatric patients. Data extraction was performed independently by two reviewers, with discrepancies resolved by a third reviewer. Risk of bias was assessed using the Newcastle-Ottawa Quality Assessment Form. The analysis included the assessment of various outcomes, such as the rate of spontaneous resolution, and identification of influential factors, including gender, age, laterality, and VUR grade.

Results: The pooled spontaneous resolution rate among pediatric patients with primary VUR was 0.42 (95% CI: 0.38 to 0.47, Tau2 = 0.26), demonstrating high heterogeneity (Q = 429.9, df = 32, $P < 0.001$, $I^2 = 93\%$). Egger's regression test indicated no publication bias ($p = 0.67$). VUR grade emerged as the most significant determinant of spontaneous resolution, with varying rates for different grades: grade 1 (0.80, 95% CI: 0.72-0.86), grade 2 (0.67, 95% CI: 0.60-0.74), grade 3 (0.49, 95% CI: 0.42-0.56), and grade 4 (0.23, 95% CI: 0.18-0.30; Tau2 = 0.28, $I^2 = 0.49$). While differences in gender and laterality were observed, statistical significance was not evident.

Conclusion: This study provides valuable insights into the spontaneous resolution rate of primary vesicoureteral reflux in pediatric patients. The constructed nomogram, based on VUR grading, serves as a useful tool for clinicians in decision-making. Despite observed variations in gender and laterality, only VUR grading demonstrated statistical significance in influencing spontaneous resolution. Further research is recommended to explore additional factors within larger populations to enhance our understanding of primary VUR resolution dynamics.

Keywords: primary vesicoureteral reflux; spontaneous resolution; pediatrics; vesicoureteral reflux grade; systematic review

INTRODUCTION

Vesicoureteral reflux (VUR) is defined as the regurgitation of urine into the upper urinary tract(1), and it occurs in approximately 40% of children who suffer from urinary tract infection (UTI). UTI is one of the most frequent bacterial infections among pediatric patients, and VUR, as a predisposing factor of UTI in this population, has been the focus of attention for years[2-4]. VUR is the fifth most common cause of chronic renal insufficiency in children. Additionally, 6% of end-stage patients who need transplantation or dialysis also suffer from vesicoureteral reflux. 17-37% of prenatally diagnosed hydronephrosis cases are caused by VUR, and 20-30% of children with VUR have renal lesions[5]. VUR is classified into primary and secondary. Primary vesicoureteral reflux defined as VUR caused by genetic components and congenital abnormalities, such as short intravesical ureter, an absent intravesical ureter, the absence of adequate detrusor backing, lateral displacement of the ureteral orifice and Para-ureteral (Hutch) diverticulum can cause primary VUR, but the mechanism of transmission is not clear[6-8]. UTI, cystitis, bladder outlet obstruction (BOO), neurogenic bladder and detrusor instability are the secondary causes of VUR. The prevalence of primary vesicoureteral reflux is approximately 1 to 2% of the pediatric population[9]. The initial AUA guidelines for VUR, published in 1998, investigated the effect of VUR grade, age, and laterality on the rate of spontaneous resolution[10]. However, subsequent studies demonstrated that the resolution rate of primary VUR resolution depends on other factors, such as gender, timing of reflux, voiding dysfunction, congenital abnormalities and presentation form. There

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Table 1. Characteristics of the included studies.

first author	country	published year	Total Sample size	gender	age	laterality grading	VUR	Reference
Amir Arsanjani	USA	2007	n=201	G: n = 46 B: n = 155	mean age ± SD 41 ± 39 months.	U: n=115 B: n=86 III: n=73 IV: n=14 V: n=2	I: n=23 II: n=89	(29)
Andrew J. Kirsch	USA	2014	n=229	G: n = 148 B: n = 81	mean age ± SD 0.46 ± 0.43 years	U: n=122 B: n=101 III: n = 82 IV: n = 35 V: n = 23	I: n = 19 II: n = 70	(24)
Arlen	USA	2017	n=147	G: n-98 B: n=49	Mean age ± SD 5.5 ± 4.7 months	U: n=59 B: n=88 III: n=51 IV: n=31 V: n=13	I: n=6 II: n=46	(27)
Brok	US	1983	n=65 patients with cystitis follicularis	G: n=62 B: n=3	- U: n=37 B: n=28	I: n=14 II A and B: n=36 III: n=10 IV: n=5		(30)
Chang	Korea	2009	n=89	G: n=23 B: n=66	Median (range) 7 months (1 day-108 months)	U: n=51 B: n=38	III: n=26 IV: n=37 V: n=26	(31)
Estrada et al.	USA	2009	n=2,462	G: n=1897 B: n=565	n=1155 mean age ± SD (years) 2.1 ± 2.4 years	U: n=1,068 B: n=1,394	I: 148 II: 688 III: 1259 IV: 262 V:105	(11)
Filho et al.	Brazil	2007	n=511	G: n=417 B: n=94	n=170 Mean age 3.1 years	U: n=250 B: n=261	I: n=48 II: n=192 III: n=174 IV: n= 74 V: n=23	(32)
Fukui et al.	Japan	2013	n=276	G: n=82 B: n=194	n=173 mean age ±SD IRR group: 6.8 ± 6.3 months control group:17.3 ± 14.0 months	U: n=98 B: n=178	III: n=81 IV: n=113 V: n=82 VUR Grade	(33)
Garcia-Roig et al.	USA	2017	n=271	G: No surgery: n=182 surgery: n=68 B:no surgery: n=14 surgery: n=7	(mean ± SD, years) 4 ± 2.1 years	U: n=166 B: n=105	(median (25th-75th)) 2 (2 – 3)	(22)
Greenfield et al.	USA	1997	n=601	G: n=433 590 renal units B: n=168 245 renal units	under1: n=40, 1-3: n=80, 4-6: n=70, 7-9: n=33, 10 and older: n=7	U: n=367 B: n=234	I: n=183 ureters II: n=371 ureters III: n=176 ureters IV: n=78 ureters V: n=27 ureters	(34)
Hidehiro Kakizaki	Japan	1998	n=34	NR NR	4.6 months	U: n=10 (29%) B: n=24 (71%)	IV&V: n=19 (35)	
Huang et al.	Taiwan	1995	n=105	G: n=31 B: n=74	under1 month: n=19 1month to 1year: n=93, 1-6years: n=48, more than 6 years: n=7	U: n=43 B: n=62	I: n=13 II: n=42 III: n=81 IV: n=25 V: n=6	(26)
JYOTI UPADHYAY	canada	2003	n=25 44 renal unit	G:n=7 B:n=18	-	U: male: n=2 female: n= 4 B: male: n=16 female: n= 3	of 44 renal units I: n=3 II: n=9 III: n=15 IV: n=7 V: n=10	(36)
K. AFSHAR	Canada	2005	n=95 150 renal units	G: n=54 B: n=41	Median age 2.5 years	-	I, II: n=52 II: n=30 IV, V: n=18	(37)
KAHLID FOUDA NEEL	canada	2000	n=85	G: n=70 B: n=15	median (range) 36 months (1 - 128)	U: n=53 B: n=32	I: n=9 II: n=63 III: n=11 IV: n=2	(38)
Matthew J. Knudson	USA	2007	n=324	G: n=257 B: n=67	Median (range) boys 0.2 years (0 - 6.6) girls: 2.3 years (0 - 10.7)	B: n=164	I: n=37 II: n=165 III: n=93 IV&V: n=29 (25)	

first author	country	published year	Total Sample size	gender	age	laterality grading	VUR	Reference
Nepple.K et al.	USA	2010	n=129 IN Normal renal ultrasound: n=90 IN Abnormal renal ultrasound n=39	G: n=111 IN Normal renal ultrasound: n=78 IN Abnormal renal ultrasound n=33 B: n=18 IN Normal renal ultrasound: n=12 Abnormal renal ultrasound n=6	Age (year) Mean ± SD 2.6 ± 2.3 In Normal renal ultrasound: 2.8 ± 2.3 In Abnormal renal ultrasound 2.2 ± 2.1	U: n=69 (53%) B: n=60 (47%) IN Normal renal ultrasound: n=39 (43%) IN Abnormal renal ultrasound n=21 (54%)	I: n=18 II: n=67 III: n=36 IV: n=8	(39)
Nepple.K et al.	USA	2008	161	G n=127 B: n=34	-	U: n=81 B: n=80	I: n=18 II: n=73 III: n=51 IV/V: n=19	(40)
Nepple.K et al.	USA	2008	n=161	G: n=127 B: n=34	Age at diagnosis Mean ± SD 2.3 ± 2.2	U: n=81 B: n=80	I: n=18 II: n=73 III: n=51 IV/V: n=19	(41)
Papachristou.fetal	Greece	2004	n=109 176 renal units	G: n=34 B: n=75	n=109 mean ± SD 6.15 ± 3.4 months	U:n=75 B: n=67 male: n=44 female: n=23	-	(42)
Papachristou.fetal	Greece	2006	n=186 302 renal units	G: n=83 B: n=103	n=186 mean (range) 5.97 months (1–12).	U: n=70 B: n=116	renal units I: n=6 II: n=148 III: n=116 IV: n=27 V: n=5	(43)
Payza a. et al	Turkey	2019	n=350	G: n=226 B: n=124	median age 5 years male: 3 years range (5 days-16 years) female: 5 years range (8 days-18 years)	U: n=214 B: n=169	right I: n=38 II: n=49 III: n=93 IV: n=53 V: n=24 left I: n=20 II: n=53 III: n=111 IV: n=94 V: n=17	(44)
Peer Wildbrett	Germany	2013	n=62 (83 renal units)	G: n=45 B: n=21	Median (range) group one 2 months (0-9 months). Median (range) group two 4 years (1-10 years)	U:21(34%) B:41(66%)	I: n=11 II: n=18 III: n=22 IV: n=14 V: n=2	(28)
peppas d. et al	USA	1991	n=602 surgical group: n= 32 non-surgical group: n=24	G: of 56 duplicated n=48 B: of 56 duplicated n=8	mean surgical group 3.1 years non-surgical group 1.4 years	U: of 56 duplicated n=42 B: of 56 duplicated n=14	single system out of 844 ureters I: n=56 (6.6%), II: n=457 (54.1%), III: n=267 (31.6%), IV: n=48 (5.7 %), V: n=16 (1.9%) Duplicated system out of 70 ureters I: n=4 (5.7%) II: n=28 (40%) III: n=19 (27.1%) IV: n=11 (15.7%) V: n=8 (11.4%)	(45)
PRAYONG VACHVANICHSANONG	thailand	2006	n=87	G: n=46 65 ureter B: n=41 68 ureter	-	B: n=53	renal unit I: n=26 II: n=22 III: n=47 IV: n=26 V: n=12	(46)
Prisca r. et al	Romania	2017	n=202	G: n=123 B: n=79	n=43 median (range) 28.5 months (1 - 192)	B: n=59	II: n=72 III: n=62 V: n=6	(47)
R. WEISS	USA	1992	68	G: n=58 B: n=10	(Years) less than 2: n= 22 2-6: n=31 6-10: n=15	U: n=33 B: n=34	0/III n=7 0/IV n=26 Less than III/III n=0 Less than III/IV n=8 III/III n=2 III/IV n=12 IV/IV n=12	(48)
R.S. Zee (49)	USA	2006	179	G: n=42 B: n=137	-	U: n=86 B: n=93	of 153 subjects SFU grade 0: 4 (3%) SFU grade 1: 31 (20%) SFU grade 2: 84 (55%) SFU grade 3: 22 (14%) SFU grade 4: 12 (8%)	
Sarhan O. et al	Egypt	2020	n=68	G: n=36 B: n=32	mean ± SD (range) 10 ± 8.5 months (1–32)	all unilateral	I: n=11 II: n=22 III: n=20 IV: n=8	(50)

first author	country	published year	Total Sample size	gender	age	laterality grading	V: n=7 VUR	Reference
Seung Joo Lee	Korea	2015	n=128 Probiotics: n=64 Antibiotics: n=64	G: probiotic: n=26 antibiotic: n=20 B: probiotic: n=38 antibiotic: n=44	all aged 1 week to 12 months Probiotics: 4.7 ± 3.6 months Antibiotics: 5.9 ± 5.5 months	NR NR	probiotic: I: n=4 II: n=8 III: n=29 IV: n=19 V: n=4 antibiotic: I: n=7 II: n=4 III: n=24 IV: n=23 V: n=6	(51)
Silva M. et al	brazil	2005	n=53 83 renal units	G: n=12 B: n=41	n=53 mean (range) 2 months (1-18)	U: n=22 (43.4%) B: n=30 (56.6%)	I: n=4 II: n=10 III: n=22 IV: n=24 V: n=23	(52)
SPENCER BARTHOLD	USA-Spain	1999	n=107	G: n=54 B: n=53		U: n=44 B: n=63	not repoted properly	(53)
STEVEN J. SKOOG	USA	1987	n=545 844 renal unit	G: n=467 B: n=78	mean age nonsurgical group (n=468) nonsurgical group 3.16 years surgically treated group (n=77) 4.55 years	U: n=245 B: n=300	I: n=20 II: n=266 III: n=165 IV: n=15 V: n=2 surgical group I: n=0 II: n= 6 III: n=36 IV: n=21 V: n=14	(54)
Victoria L. Troesch	usa	2021	n=136	G: n=93 B: n=43	mean age ± SD (range) 2.32 ± 2.17 years (0-9)	U: n=70 B: n=63	I: n=12 II: n=61 III: n=41 IV and V: n=22	(55)
Zeliha Ural	turkey	2008	n=155	G: n=125 B: n=30	mean age ± SD (6.5 ± 2.8) years Boys 1-5 years n=7 older than 5 years n=23(44%) girls 1-5 years n=55 older than 5 years n=70	B: 1-5 years n=1 older than 5 years n=9 B:girls 1-5 years n=18 older than 5 years n=20	I: 19% II: 22% III: 33% IV: 16% V: 9%	(56)

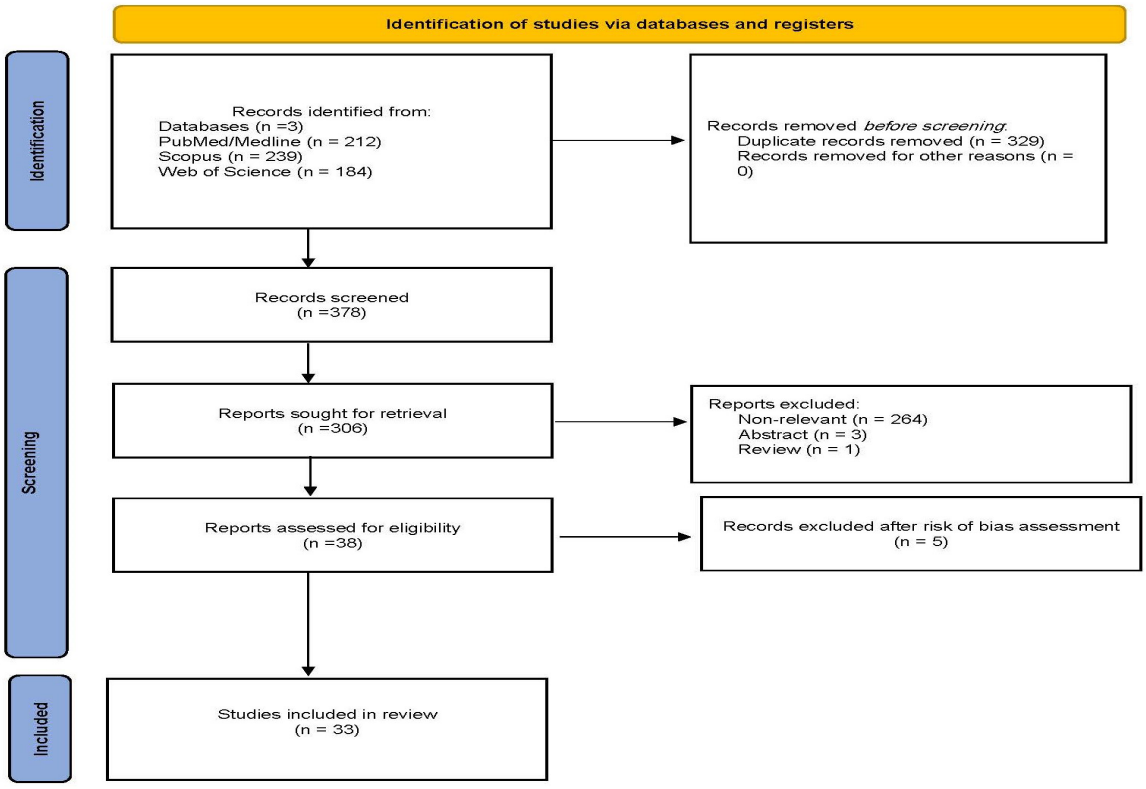

Figure 1. Prisma Flowchart

Table 2. Newcastle-Ottawa Quality Assessment.

first author	Selection	representative of the exposed cohort	selection of external cohort	outcome of interest not ascertainment of exposure	Comparability	main factor present at the start of the study cohort	additional factor	Outcome	assessment of outcomes	sufficient follow up time	adequacy of follow up	good, fair, and poor	
Kakizaki	4	*	*	*	*	1	*	3	*	*	*	good 8	(35)
Andrew J. Kirsch	4	*	*	*	*	2	*	*	3	*	*	good 8	(24)
Matthew J. Knudson	4	*	*	*	*	1	*	3	*	*	*	good 8	(25)
Seung Joo Lee	4	*	*	*	*	2	*	*	3	*	*	good 8	(51)
KAHLID FOUDA NEEL	4	*	*	*	*	2	*	*	3	*	*	good 8	(38)
Nepple.K et al.	4	*	*	*	*	1	*	2	*	?	*	good 8	(39)
Nepple.K et al.	4	*	*	*	*	2	*	*	3	*	*	good 8	(40)
Nepple.K et al.	4	*	*	*	*	1	*	2	*	*		good 7	(41)
Papachristou.fetal	4	*	*	*	*	2	*	*	3	*	*	good 9	(42)
Papachristou.fetal	4	*	*	*	*	2	*	*	3	*	*	good 9	(43)
Payza a. et al	4	*	*	*	*	1	*	2	*	*	*	good 7	(44)
Silva M. et al	4	*	*	*	*	1	*	3	*	*	*	good 8	(52)
peppas d. et al	4	*	*	*	*	1	*	3	*	*		good 7	(45)
Prisca r. et al	4	*	*	*	*	2	*	*	2	*	*	good 8	(47)
Sarhan O. et al	4	*	*	*	*	2	*	*	3	*	*	good 9	(50)
Estrada et al.	4	*	*	*	*	1	*	3	*	*	*	good 8	(11)
Filho et al.	4	*	*	*	*	1	*	3	*	*	*	good 8	(32)
Fukui et al.	4	*	*	*	*	1	*	3	*	*	*	good 8	(33)
Garcia-Roig et al.	3	*		*	*	1	*	1		*		poor 5	(22)
Greenfield et al.	4	*	*	*	*	2	*	*	3	*	*	good 9	(34)
Huang et al.	4	*	*	*	*	2	*	*	3	*	*	good 9	(26)
K. AFSHAR	4	*	*	*	*	1	*	3	*	*	*	good 8	(37)
Arlen	4	*	*	*	*	2	*	*	3	*	*	good 8	(21)
Amir Arsanjani	4	*	*	*	*	2	*	3	*	*	*	good 8	(29)
SPENCER BARTHOLD	4	*	*	*	*	0		3	*	*	*	fair 7	(53)
Brok	4	*	*	*	*	0		2	*		*	poor 6	(30)
Chang	2		*		*	1	*	1	*			poor 4	(31)
STEVEN J. SKOOG	4	*	*	*	*	2	*	*	3	*	*	good 9	(54)
Victoria L. Troesch	4	*	*	*	*	2		3	*	*	*	good 7	(55)
JYOTI UPADHYAY	4	*	*	*	*	1	*	3	*	*	*	good 8	(36)
Zeliha Ural	4	*	*	*	*	2	*	*	3	*	*	good 8	(56)
PRAYONG VACHVANICHSANONG	4	*	*	*	*	2	*	*	3	*		good 9	(46)
R. WEISS	4	*	*	*	*	0		3	*	*	*	fair 7	(48)
Peer Wildbrett	4	*	*	*	*	2	*	*	3	*	*	good 9	(28)
R.S. Zee	4	*	*	*	*	1		*	3	*	*	good 7	(49)

are 5 stages of VUR (IV-V), of which high stages can cause serious renal damage[11]. Various strategies exist to prevent recurrent UTIs and subsequent renal scarring in VUR patients. Prophylactic antibiotics and watchful waiting have been reported to be effective in some cases, while surgery might be necessary in others[12-16]. The estimated cost of treating children of all grades is about 302,024$ per year based on quality-adjusted life-year (QALY), whereas preventive methods could save approximately 37,903$[17]. Scanning with the 99mTechnetium-dimercaptosuccinic acid (99mTc-DMSA) method is commonly used to diagnose reflux and reported to be the most sensitive test for detecting focal kidney abnormalities and scars. There are three management methods for treating VUR: active surveillance, medical treatment, and surgical treatment. Spontaneous resolution of primary VUR is a common outcome, suggesting that medical management should be favored over unnecessary surgical interventions. Physicians aim to minimize overtreatment and prevent renal scarring in patients at low risk of urinary tract infection[11].
Considering that the efficacy of treatment management is related to factors such as sex, age, disease progression, and underlying factors[10,11], there is currently insufficient information to guide clinicians efficiently in predicting spontaneous resolution rates in patients with primary VUR. This study aims to evaluate the factors including sex, age, grading and underlying factors to predict the rate of spontaneous resolution. Data is extracted via a systematic review of previously published studies focusing on the spontaneous resolution of primary VUR patients.

MATERIALS AND METHODS

Search Strategy

Upon receiving approval from the ethics committee and research board of the university, the systematic review process began. Our search was initiated on 17 February 2022. We conducted searches on PubMed, Web of Science, and Scopus. The following search terms were used: (((medical management[tw]) OR (medical treatment[tw])) OR (watchful waiting[tw] OR"resolution"[tw])OR"spontaneous resolution"[tw]) AND ((primary[TW]) AND ("Vesico-Ureteral Reflux"[Mesh])). Online database searching began on 17 February 2022 and was updated on September 2023 to investigate newly published articles.

Selection criteria

The article selection was conducted according to the search strategy recommended in the Preferred Reporting Items for Systematic Reviews and Meta-analyses criteria (PRISMA). The search and selection criteria were not restricted to the English language. We were looking for all the clinical trials, including cohort studies, that reported the spontaneous resolution rate of primary VUR and associated factors. Reviews, letters, case reports/series, correspondences, abstracts, and studies only reporting surgical intervention outcomes were excluded. However, studies with a control group utilizing a conservative approach were included for data extraction. Initially, all studies from different databases were merged, and duplicates were removed. YK and NN independently conducted the initial screening independently, and PF was the third person to vote on conflicts and review the final selection of studies. Full texts of the remaining studies were then carefully reviewed by two independent individuals, and the data were collected. PZ was responsible for reviewing the entire extracted data (**Figure 1**). The reference lists of the retrieved studies were also explored.

Data extraction

The following data were extracted from each study and organized into an Excel spreadsheet (Microsoft, Redmond, WA): first author's name, country, year of publication, total number of participants, and data of patients with spontaneous resolution rate including gender, age, laterality, and VUR grading. (**Table 1**)

Risk of Bias Assessment

The quality and risk of bias of the included studies were assessed and scored by two independent individuals using the "Newcastle-Ottawa Quality Assessment Form for Cohort Studies". All disagreements were resolved through discussion. (**Table 2**)

Statistical methods

The effect size of interest was the spontaneous resolution rate. The random-effects model was employed for the analysis. The studies in the analysis were assumed to be a random sample from a universe of potential studies, and this analysis will be used to make an inference to that universe. The Q-statistic provides a test of the null hypothesis that all studies in the analysis share a common effect size. If all studies shared the same true effect size, the expected value of Q would be equal to the degrees of freedom (the number of studies minus 1). Using a criterion alpha of 0.100, we could reject the null hypothesis that the true effect size was the same in all these studies. The I-squared statistic represents the variance in observed effects that reflects variance in true effects rather than sampling error. The greater value points to greater heterogeneity (18). Tau, the standard deviation of true effect sizes in logit units, was used to make prediction intervals. The statistics were presented with a 95% interval. Statistical analysis was performed by CMA-V4 package (USA, August, 2022).

RESULTS

Among all 378 studies which have been screened by two individual reviewers, 72 papers were duplicated. Of all unique studies 264 studies were excluded regarding title, abstract or full text and 38 studies have been approved regarding that matter. After full text screening and quality assessment, by the Newcastle Ottawa questionnaire, 33 full text studies were included. Four main topics for data extraction were, gender, age, laterality, and grade. Each study has been reviewed to extract the relevant data regarding these topics. Detailed data can be found in **Figure 1**.
A total of 33 relevant studies have been included. Each of these studies aimed to determine whether these factors could predict the outcome of primary VUR. Laterality, gender and VUR grades' effects on primary VUR resolution were discussed in 5, 8, and 22 studies, respectively. These studies provide a sufficient amount of quantitative data on this matter, enabling us to conduct a meta-analysis on the effects of these factors on the spontaneous resolution of VUR. Detailed data can be found in **Table 1**.
There were 33 studies reporting spontaneous resolution rates for primary VUR, including 8540 patients consisting of 75 subgroups for gender, grade, and laterality. Also, a separate analysis was performed for the iden-

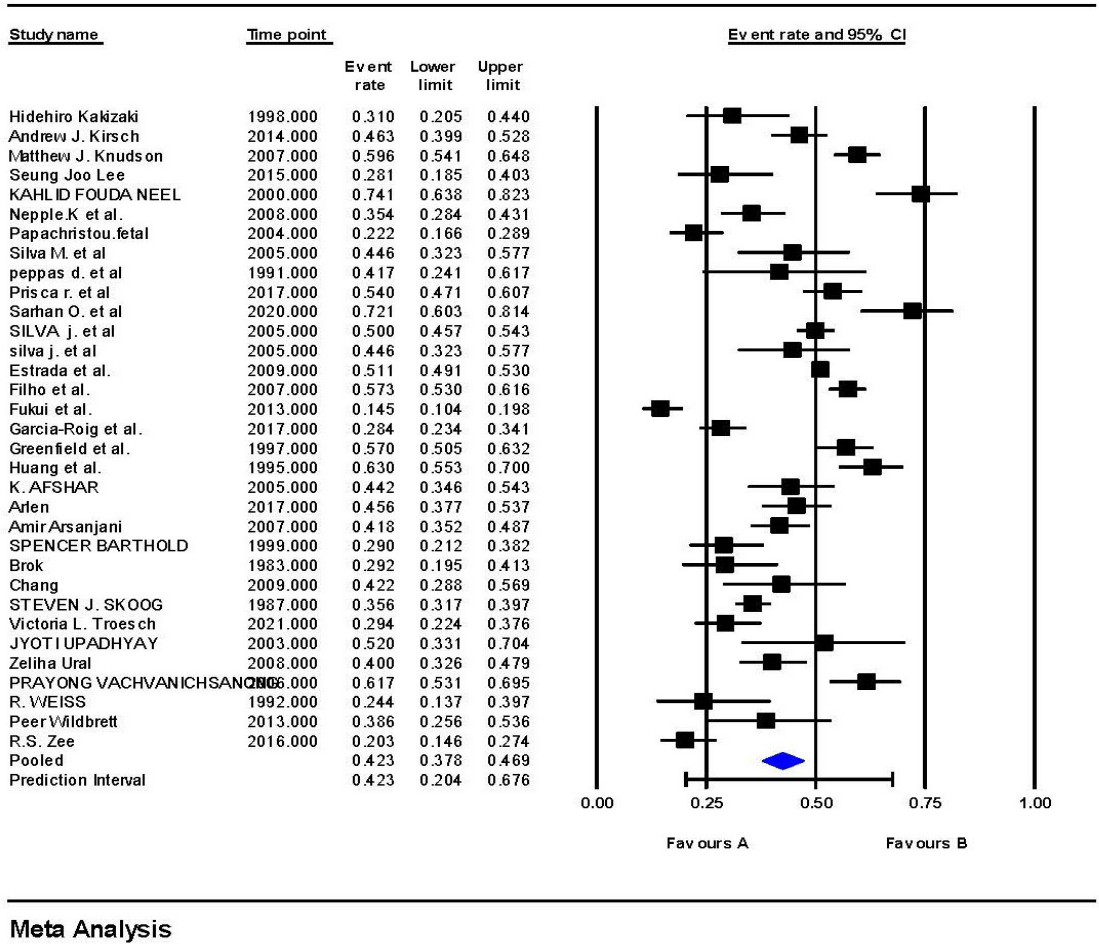

Figure 2. Pooled spontaneous resolution rate among the included studies with random effect model (REM)

tified groups having under 1 year of age (**Figure 2-B**). The pooled spontaneous resolution rate was 0.42 (95% CI: 0.38 to 0.47, Tau2 = 0.26) though with high heterogeneity between studies (Q = 429.9, df = 32, $P < 0.001$, I2=93%) Egger's regression test ($p = 0.67$), there is no publication bias (**Figure 2**).

Gender

According to subgroup analysis, spontaneous resolution rate was greater in females; however, the difference was not significant. The rate was 0.56 (0.40-0.67) in females and 0.49 (0.35-0.63). (Tau2 = 0.49, $I^2 = 0.80$) in males (**Figure 3-A**). Comparing females and males less than 1 year of age, did not reveal any significant difference between genders (Figure 3-B).

Laterality

Pooled spontaneous resolution rate was 0.33 (0.21-0.48) in bilateral and 0.53 (0.38-0.68) in unilateral cases (Tau2 = 0.33, $I^2 = 87\%$). (**Figure 4**). Then, the lower spontaneous resolution rate in bilateral cases could not be approved.

Grade

VUR grade was the most significant determinant of spontaneous resolution in the evaluated studies. For grade 1 the pooled rate was 0.80 (0.72-0.86), for grade 2 it was 0.67 (0.60-0.74), for grade 3 the pooled estimate reached to 0.49 (0.42-0.56) and for grade 4 it was 0.23 (0.18-0.30). (Tau2 = 0.28, $I^2 = 0.49$). (Figure 5) In other words, the worst grades had a significantly lower resolution rate compared to the lower grades.

DISCUSSION

Some factors could lead to severe conditions of VUR and make the resolution time longer. In this study, we chose three aspects of VUR and did a meta-analysis on them. Here we discuss the results of our meta-analysis and further discuss differences and similarities between our findings and other meta-analyses.

Laterality

For laterality, four studies were included. Unilaterality and bilaterality were analyzed independently and then pooled. Unilaterality of VUR as independent factor showed no significant relation with resolution time. This data again was repeated in bilateral VURs and found no significant relation between bilateral VURs and resolution time. The pooled result found the same result. No significant connection was between laterality and resolution time. C. WILLIAM SCHWAB et al found a different result. Based on their study, unilateral grade I to III had a significantly faster resolution than bilateral grade I to III reflux[19]. Sofia Sjöström et al supported our analysis. In their analysis, they found no significant relation between bilateral or unilateral cases of VUR and resolution time which supports our finding

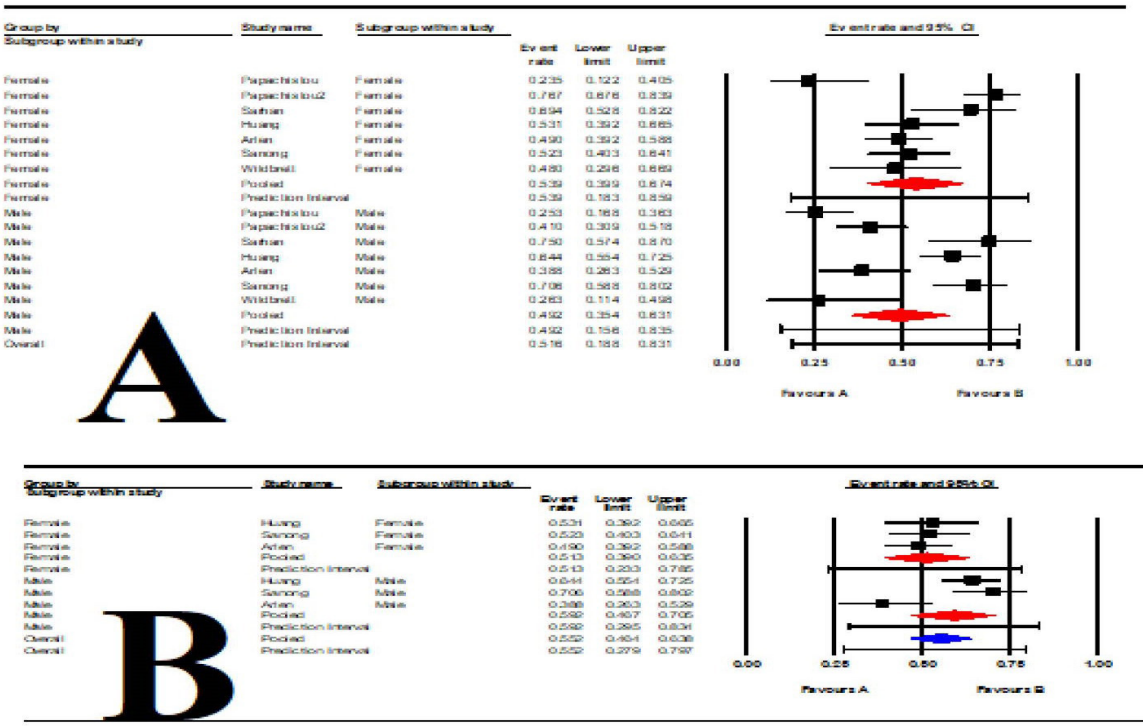

Figure 3:A. Meta-analysis of the Gender impact on the resolution rate, REM. **B:** Comparison of males and females resolution rate under 1 year of age with random effect model

[20]. Arlen et al investigate multiple factors that can be associated with the resolution of VUR. They managed to conduct the study on 304 patients with a mean age of 1.55 years old. They found that children with unilateral VUR meaningfully have a higher chance of spontaneous resolution which indeed supports our results[21]. Garcia-Roig did research to find the factors associated with the resolution of VUR and they found supportive results in favor of our findings. 271 patients were eligible with a mean age of 4 years old. In their study, laterality was not a significant factor influencing spontaneous resolution of VUR[22].

Gender

Gender was chosen as an important factor for meta-analysis. 7 studies were included. Male and female cases were analyzed independently and then pooled together. Female gender was not a significant factor for resolution time. This analysis again found no connection between male gender and resolution time. The pooled result found no connection between gender and spontaneous resolution of VUR. C. WILLIAM SCHWAB et al finding was in contrast to our finding. Based on their study, male gender has tendency to faster resolution than the female gender[19]. Sofia Sjöström et al partially supported our analysis result. In their result, they could not find the connection between gender and resolution time. The partial part was that their study found this result only in grade three and lower grades of reflux and it was not a general finding[20]. Garcia-Roig research found results in contrast to our findings. 271 patients were eligible with the mean age of 4 years old. In their study, female gender was a significant factor influencing lower rate of spontaneous resolution but they noted that female gender influence only lasts in first 12 months of follow up from diagnosis[22]. In Carlos R. Estrada et al gender were analyzed with the combination of laterality. In this study resolution time of unilateral female cases of VUR is faster than bilateral female cases of reflux which indeed is not a supportive result [11]. SOFIA SJÖ STRÖM et al found an interesting result. They found no significant relation between gender and resolution time in low grade reflux (grade two and under) but at the same time they found exactly different relation for high grade reflux. In high grade VUR, male gender was found to be a good prognostic factor and male cases had a significant shorter resolution time which indeed was interesting[23]. Kirsch et al. performed an analysis with multi factors on outcomes from 229 patients diagnosed with VUR under the age of 2 years. They were diagnosed by VCUG screening. The researchers reported that female patients had significantly longer time to spontaneous resolution indicating a negative relation between female gender and spontaneous resolution of vesicoureteral reflux which indeed is in contrast with our findings[24].

Grade

Twelve studies discussed grade as a key factor. Each grade was discussed as an individual factor and we compared each grade to another. In our analysis, we specified three main finding. First, we found no meaningful difference between grade I and II. Second, we determined that grade IV of VUR will be meaningfully worse than grade III in resolution. Lastly, we found that both grade IV and III are negative factors in resolution compared to grade I and II. C. William Schwab et al found similar results in their study, demonstrating that grades I to III of reflux will resolve faster than grades IV to V reflux. This aligns with the findings of our study [19]. Arlen et al investigated multiple factors associated

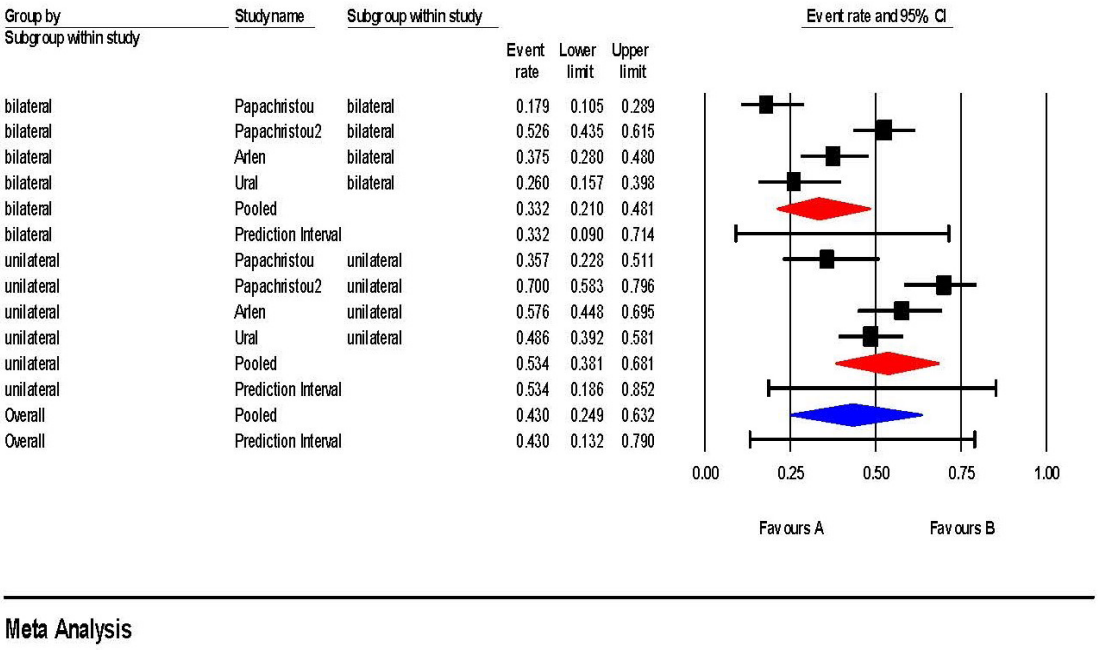

Figure 4. Forest plot of the spontaneous resolution rate in unilateral and bilateral subgroups, REM

with the resolution of VUR. Their study included 304 patients with a mean age of 1.55 years. They found that in children with grades I to III VUR, there is a significantly higher chance of spontaneous resolution, which aligns with our results[21]. Another study conducted by Carlos R. Estrada et al also found similar results. In this article, grades I to III of reflux had a significantly faster resolution than grades IV to V reflux, which supports our findings[11]. Furthermore, Matthew J. Knudson et al identified a positive correlation between a lower grade of reflux and a shorter resolution time[25]. In another study, Kirsch et al. conducted a multivariate analysis on outcomes from 229 patients diagnosed with VUR under the age of 2 years, using VCUG screening for diagnosis. The researchers reported that patients with grade IV–V of VUR had a significantly longer time to spontaneous resolution, indicating a negative relationship between high-grade VUR and the spontaneous res-

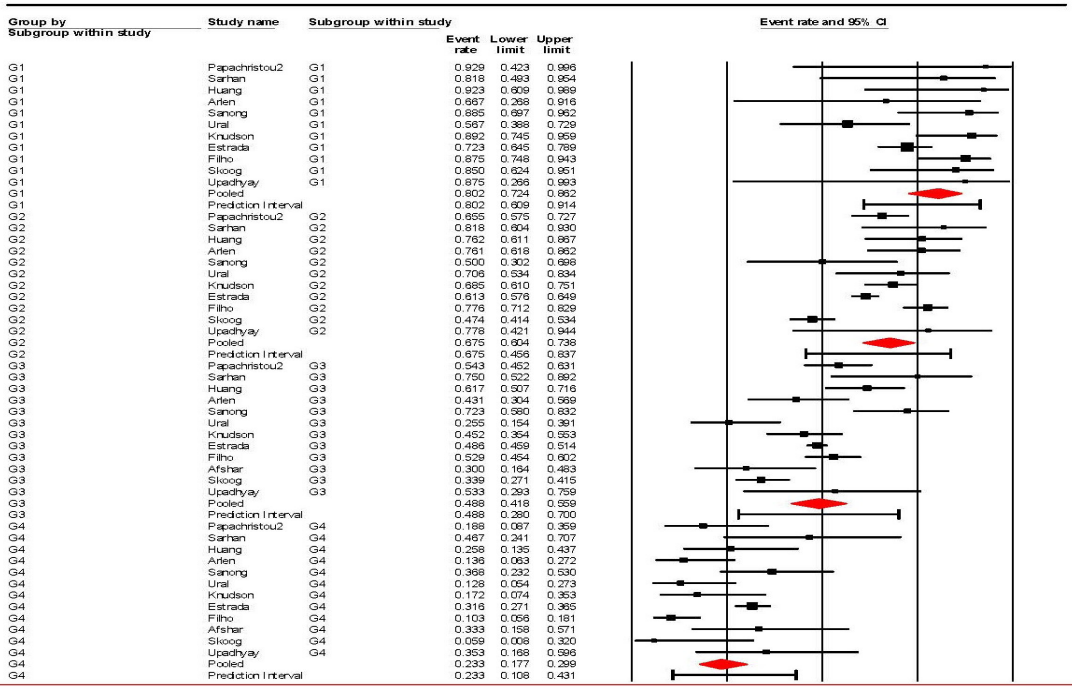

Figure 5. Estimation and comparing the spontaneous resolution rate in various grades by REM

olution of VUR[24].

Age

Vesicoureteral reflux (VUR) is a prevalent condition in children. Notably, a study conducted by Huang et al.[26] , involving 105 individuals, revealed that VUR spontaneously resolves in varying proportions across age groups: 63.2% in infants under 1 month, 64.5% in children between 1 month and 1 year, 58.3% in children aged 1 to 6 years, and 28.6% in children older than 6 years. Additionally, Arlen et al. classified 147 children into two groups: those under one year (131 patients) and those over one year (16 patients). The percentages of spontaneous resolution were 47.3% and 31.2%, respectively[27]. In alignment with previous research, Peer Wildbrett et al. conducted a 10-year single-center study involving 83 renal units in 62 patients. They found that the resolution rate for children under 1 year old was 17 out of 44 renal units (38.6%), and for children over 1 year old, it was 9 out of 23 renal units (39.1%). To provide a more comprehensive perspective, presenting these results in terms of both the number of patients and renal units would be insightful. In summary, it can be deduced that the likelihood of VUR resolution is higher in younger children, particularly those under 1 year of age. As children age, the probability of spontaneous recovery decreases[28].

CONCLUSIONS

Given the heterogeneity of data related to factors beyond gender, laterality, and grade, a comprehensive analysis of additional influences on spontaneous vesicoureteral reflux was unfeasible. This study specifically examined three predisposing factors affecting the spontaneous resolution rate of primary vesicoureteral reflux, with statistical significance observed solely in VUR grading. While variations were noted in gender and laterality, statistical significance was not established. Future research endeavors should delve into and assess various factors within larger populations to gain a more nuanced understanding.

CONFLICT OF INTEREST

The authors report no conflict of interest.

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