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ORIGINAL ARTICLE

Diagnostic accuracy of contrast-enhanced voiding urosonogram using second-generation contrast with harmonic imaging (CEVUS-HI) study for assessment of vesicoureteral reflux in children: a meta-analysis

Michael E. Chua[1] · Jonathan S. Mendoza[1] · Jessica M. Ming[2] · Jun S. Dy[1] · Odina Gomez[3]

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Abstract

Purpose To assess the diagnostic accuracy and safety of contrast-enhanced voiding urosonogram using second-generation contrast with harmonic imaging (CEVUS-HI) in detecting vesicoureteral reflux (VUR) among children.

Methods A systematic literature search was performed in March 2018. Relevant comparative studies from Medline, EMBASE, World of Science, Scopus, CENTRAL, WHO trial registry and Clinicaltrials.gov were identified and appraised using QUADAS-2. Diagnostic accuracy parameters were determined using VCUG as the reference standard. Adverse effects related to ultrasound contrast were summarized. The heterogeneity and inter-study variability were determined. After appropriate subgroup diagnostic accuracy parameters were investigated, summarizing receiver operator characteristics was constructed using the bivariate model meta-regression to determine the area under the curve (AUC).

Results A total of 12 studies with low–high risk of bias, including 1917 ureteral units from 953 patients were assessed for this meta-analysis. The included studies reported no serious adverse events associated with the ultrasound contrast. The pooled diagnostic accuracy parameters of CEVUS-HI in detecting VUR amongst children were: sensitivity 90.43 (95% CI 90.36–90.50), specificity 92.82 (95% CI 92.76–92.87), the calculated (+) likelihood-ratio 12.59 (95% CI 12.49–12.68), (−) likelihood-ratio of 0.103 (95% CI 0.102–0.104) and extrapolated pooled diagnostic odds-ratio was 122.12 (95% CI 120.75–123.49). Heterogeneity with interstudy variability was noted ($p < 0.0001$, I-squared > 70%). The AUC was determined to be 0.965 for VUR detection.

Conclusions The pooled diagnostic accuracy parameters from low–moderate quality of evidence have illustrated that the CEVUS-HI study has an excellent safety profile and acceptable diagnostic accuracy. It may be considered as an alternative diagnostic modality for assessment of VUR among children.

Keywords Contrast-enhanced voiding urosonogram · Diagnostic accuracy · Vesicoureteral reflux · Voiding cystourethrogram

Introduction

Currently, as recommended by the clinical practice guidelines of the European Society of Pediatric Urology and American Urological Association, the voiding cystourethrogram (VCUG) is considered the gold standard for diagnostic imaging of VUR among the pediatric population with urinary tract infections (UTIs) [1, 2]. However, due to the ionizing radiation exposure related to VCUG, further exploration for other diagnostic modalities, such as contrast-enhanced voiding urosonogram (CE-VUS), as the potential alternative for VCUG has been initiated [3].

In recent reviews, CEVUS alone has a diagnostic accuracy of approximately 78–97% in the diagnosis of VUR [4,

Michael E. Chua and Jonathan S. Mendoza contributed equally.

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✉ Michael E. Chua
auhc_ekim@yahoo.com

[1] Section of Pediatric Urology, Institute of Urology, St. Luke's Medical Center, Quezon City, NCR, Philippines

[2] Section of Urology, Department of Surgery, University of New Mexico, Albuquerque, NM, USA

[3] Section of Pediatric Imaging, Institute of Radiology, St. Luke's Medical Center, Quezon City, NCR, Philippines

5]. Using the second-generation contrast for CEVUS has been shown to have longer stability than the first generation and is being further augmented for better diagnostic accuracy with the use of the "harmonic imaging" mode on newer ultrasound machines. Harmonic imaging is based mainly on the non-linear propagation property of US waves, thereby increasing contrast and spatial resolution. This results in clearer and smoother images, as well as the detection of a more conspicuous microbubble [6]. Hence, we hypothesize that CEVUS, using the second-generation contrast with harmonic imaging, due to its better capability than standard ultrasound to detect retrograde flow up to the upper tract, may be considered as an alternative, safe and reliable diagnostic modality to evaluate VUR among children. However, to date, there is no literature that has exclusively defined the diagnostic accuracy of CEVUS focused on using HI mode for the detection of VUR. Our study aims to evaluate the accuracy of CEVUS using second or later generation ultrasound contrast with harmonic imaging in the diagnosis of VUR among the pediatric population compared to the reference standard VCUG.

Methodology

This meta-analysis was registered in our institutional research board (IRB# CT18147) and was conducted based on the recommendations of Cochrane collaboration and reporting compliant with the PRISMA-DT statements [7, 8].

A systematic literature search was conducted on March 8, 2018 through Medline, EMBASE, Web of Science, and Cochrane central register of controlled trial (CENTRAL) utilizing both Medical Subject Headings (MeSH) and free text in the retrieval of related records. An additional search for relevant articles and ongoing trials was made in Scopus, World Health Organization International clinical trials registry platform (WHO-ICTRP) and Clinicaltrials.gov using the simplified and sensitive search strategy for retrieval of related records: (Urosonogram OR Urosonography) AND Ureterovesical reflux (see ESM Appendix 1 for details of the search strategies used).

Diagnostic studies comparing the accuracy of harmonic imaging as the index modality versus VCUG as the reference were included in this meta-analysis. Furthermore, an expert in the field was contacted through e-mail for any possible unpublished studies which may be deemed eligible for inclusion. Relevant surveys, reviews, and commentaries were excluded only after cross-referencing was done for other relevant potential citations. In cases of non-English articles, translation using translate.google.com was done to determine the eligibility of the study.

Excluded from the review were studies with (a) no description of the use of the harmonic imaging mode or contrast-specific settings despite using CEVUS, (b) lack of a biochemical contrast, (c) a case-series and case report design, (d) a comparative design not using VCUG as a reference, and (e) no negative condition comparators.

Two reviewers independently screened and assessed the records for eligibility based on the titles and abstract. Another two rounds of screening and assessment were performed independently by the two reviewers for further identification of eligible studies. Full text of the tagged studies as per the recommendation of the reviewers was obtained to assess eligibility based on the inclusion and exclusion criteria. Included studies were then subjected to methodological quality assessment.

Critical appraisal of the methodological quality was done using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool (ESM Appendix 2). The tool consists of four key domains namely (1) patient selection, (2) index test, (3) reference study, and (4) patient flow through the study. The domains are assessed to determine the risk of bias and applicability of the index diagnostic modality. Risk of bias was defined as "low", "high" or "unclear" based on the appraisal of the reviewer [9, 10].

The data pertaining to sex ratio, age range, contrast utilized, reaction to contrast and VUR grading were extracted and summarized for each included study. A 2×2 table containing true positive (TP), false positive (FP), true negative (TN), and false negative (FN) values were either directly lifted from each study if the raw data was given and encoded based on the ureteral units (UU), or were indirectly derived using Revman5 reverse calculation if only the test for accuracies such as sensitivity and specificity were reported [10]. These values were then encoded and pooled on the meta-disc program for assessment of threshold effect and co-variate interactions [11]. The inter-study heterogeneity and variability were tested using Chi-squared and I-square, respectively, using meta-disc program. Significant heterogeneity was defined as p value <0.1 and I-square $>40\%$. Univariate meta-regression was performed to assess the effect of diagnostic threshold, study quality domains and contrast as covariate causing heterogeneity. Sensitivity analysis was attempted when an adequate number of studies allowed assessment of the robustness of the meta-analysis based on covariates causing heterogeneity.

For the analysis of data, a forest plot of the overall pooled diagnostic accuracy estimates and corresponding 95% confidence intervals (CI) was then encoded and obtained from the RevMan5 [10]. A modification of exact binomial rendition of bivariate mixed-effects regression model adapted for synthesis of diagnostic test data was employed [12]. The use of this method preserves the two-dimensional nature of the data and accounts for the correlation between diagnostic indices, rather than transforming individual study's pairs of sensitivity and specificity into a single indicator of diagnostic

accuracy. Using this model, estimation of the mean logit sensitivity and specificity, with their standard errors (SEs) and 95% CIs, estimates of the between-study variability in logit sensitivity and specificity, as well as the covariance between them, is achieved. These quantities are then reverted back to the original receiver operating characteristics (ROC) scale to derive the sensitivity, specificity, likelihood ratios and diagnostic odds ratio (dOR). The derived logit estimates of sensitivity and specificity and their respective variances are used to construct an SROC curve for CEVUS-HI, with summary operating points for sensitivity and specificity on the curve and a 95% confidence contour ellipsoid. The final SROC curve was configured using the bivariate regression parameters encoded into the RevMan5 to plot the diagnostic accuracy considering the sensitivity in relation of 1-specificity and area under the curve (AUC) was calculated. An AUC value of 0.91–1.0 was equivalent to excellent, 0.81–0.9 was equivalent to good, 0.71–0.8 was equivalent to fair, 0.61–0.7 was equivalent to poor, and less than 0.61 was equivalent to failure. To assess the presence of publication bias, Metadisc package of R project was used to generate a funnel plot of the standard error of log (dOR) against the dOR. Further statistical analysis for plot asymmetry was performed using the Macaskill modification of Egger's regression method, which is a multiplicative dispersion model using study size as the independent variable with consideration of heteroscedastic effect [12, 13].

Results

A total of 481 relevant records were retrieved from the literature search. After removal of duplicate records, 426 were screened for eligibility. After two rounds of screening, 39 full-text articles were retrieved for the final assessment of inclusion eligibility. Twenty-seven studies were excluded for reasons stated in Supplementary Figure 1. Twelve studies were eligible for qualitative and quantitative review and meta-analysis [14–25].

Study characteristics

Table 1 summarizes the characteristics of the included studies. All studies utilized second or later generations of ultrasound contrast, particularly the sulfur hexafluoride lipid-type A microsphere (Sonovue, Bracco, Milan, Italy) [14–24] or the Perflutren Protein-type A microsphere (Optison, GE Healthcare AS, Oslo, Norway) [25]. Variable dosing protocols as to the infusion of Sonovue were described. However, the most common protocol used was the infusion of 1 ml contrast after 1/3 of bladder capacity [(age in years + 2) × 30] was achieved. Optison, on the other hand, was prepared to 0.2% dilution in 100 ml saline, then infused by gravity to bladder capacity. Repeat or additional doses were given as needed to further visualize the contralateral side or voiding phase. The majority of the included studies describes expected adverse events, of which none were reported (Table 1).

The age of the recruited patients in the included studies ranged from 6 days to 17.5 years old. Most studies described the underlying reason for screening or investigating VUR, which included: urinary tract infection, dilation of the upper urinary tract, suspected VUR due to a neurogenic condition, positive family history, as well as follow-up assessment for VUR.

Study methodological quality (QUADAS-2)

Overall, the comparative studies included for this meta-analysis were assessed to be of low to high risk of bias. A summary of the study quality assessment based on the QUADAS-2 tool is presented in Supplementary Figure 2.

Diagnostic accuracy of index test

A total of 1917 ureteral units were derived from 953 patients recruited by the included studies. VUR was detected by VCUG in 508 (26.4%) ureteral units, while 635 (33.1%) were classified as VUR positive by the CEVUS-HI. Initial pooling of diagnostic accuracy parameter performed in Metadisc using DerSimonian–Laird method detected significant heterogeneity with large inter-study variability within the included studies (Chi-squared p value < 0.0001, I-squared $> 70\%$) (Supplementary Figures 3–5). To assess possible sources of heterogeneity, a univariate meta-regression was performed with each study domain's risk of bias considered as variables. This revealed no statistical significance among the study domains (Supplementary Table 1). Further assessment of the diagnostic threshold using the Spearman correlation coefficient between sensitivity and specificity, similarly, showed no statistical significance (Spearman $r = 0.018$, $p = 0.957$). Using Moses–Shapiro–Littenberg's model with restricted maximum likelihood estimation, showed no statistical significance with the dOR being constant and suggestive of diagnostic accuracy not being related to any threshold effect (Tau squared estimate 1.4344, $p = 0.933$).

The overall pooled diagnostic accuracy parameters generated using bivariate mixed-effects regression model for CEVUS-HI based on VCUG as the reference, determined a pooled sensitivity 90.43 (95% CI 90.36–90.50), specificity 92.82 (95% CI 92.76–92.87) (Fig. 1). The calculated positive likelihood ratio 12.59 (95% CI 12.49–12.68) and negative likelihood ratio 0.103 (95% CI 0.102–0.104); while the extrapolated pooled dOR was 122.12 (95% CI 120.75–123.49). Using bivariate regression parameters the

Table 1 Summary of included studies characteristics

References	Population	Total number of patient	Total reno-ureteral unit	Sex ratio (M:F)	Indication for VUR investigation	VCUG detail	Ultrasound–harmonic imaging setting	Ultrasound contrast used	Infusion method of contrast	Micturition cycle studied	Adverse event
Ascenti et al. [14] Italy	3 months–5-year-old	80	160	36:44	UTI, uretero-pelvic dilation, follow-up for VUR treatment	Described the VCUG performed following the guidelines suggested by the International Reflux Study in Children. No cyclic bladder filling was conducted in this study	Technos MPX US scanner (Esaote, Genoa, Italy) with alternating tissue harmonic mode and 'CnTI', contrast-specific second harmonic software. Mechanical index: 0.3–0.7 for tissue-harmonic mode 0.04–0.67 for contrast-specific second-harmonic mode	Sonovue (0.5 ml in 4.5 ml saline), 0.5 ml bladder instillation per cycle	Slow intravesical instillation after 1/3 of total bladder capacity was achieved	1 cycle (no mention of procedure duration	No mention
Papadopoulou et al. [15] Greece	6 days–13-year-old	228	463	123:105	UTI, follow-up of VUR, antenatal urinary tract dilation, sibling of child with VUR	Cyclic VCUG was performed with a digital fluoroscopic system at the same session immediately after the end of VUS using the same catheter. Intermittent pulsed fluoroscopy was performed in all cases. The bladder was filled with iodinated contrast medium (Iopromide, Ultravist 300 mg/ml diluted with normal saline (1:3) at body temperature by drip infusion (80 cm from the top of examination bed). Two films during the filling phase, one or two during voiding and one after voiding, were taken. The catheter was left in the bladder during voiding to be used for the second filling of the bladder. Graded according to the International Reflux System of grading	Esatune 570 FD high-definition scanner, (Esaote. Milan, Italy) equipped with HI mode and 'CnTI', and contrast-specific harmonic software dedicated to second-generation contrast. Mechanical index: 0.08–0.16 contrast-specific mode	Sonovue (concentration not mentioned), 1 ml intravesical administration	Intravesical administration after 1/3 of total bladder capacity was achieved	2 cycles at 15–20 min duration	Assessed, none reported

Table 1 (continued)

References	Population	Total number of patient	Total renoureteral unit	Sex ratio (M:F)	Indication for VUR investigation	VCUG detail	Ultrasound–harmonic imaging setting	Ultrasound contrast used	Infusion method of contrast	Micturition cycle studied	Adverse event
Kis et al. [16] Hungary	2 months–44 months	183	366	94:89	UTI, Pelvicalyceal dilation, follow-up for VUR	The catheter used for the VUS was left in the bladder for use during the fluoroscopic VCUG. The bladder was filled with iodinated contrast material (Optiray, 300 mg/ml iodine) diluted with room-temperature normal saline (1:5) by drop infusion (100 cm from the top of the examination bed). The bladder capacity was reached almost equally in both examinations. The presence of contrast medium in the ureter or the pelvicalyceal system was considered diagnostic of VUR and was graded according to the International Reflux System of grading. The catheter was removed during micturation	Logiq 9 high-definition scanner (GE Healthcare) equipped with HI software. Mechanical index: 0.4–0.6	Sonovue (concentration not mentioned), 1 ml intravesical administration	After leaving some urine in the bladder after catheterization, intravesical administration of contrast followed by slow bladder filling at 100 cm level from examination table	1 cycle at 8–15 min duration	Assessed, none reported

Table 1 (continued)

References	Population	Total number of patient	Total renoureteral unit	Sex ratio (M:F)	Indication for VUR investigation	VCUG detail	Ultrasound–harmonic imaging setting	Ultrasound contrast used	Infusion method of contrast	Micturition cycle studied	Adverse event
Kljucevsek et al. [17] Slovenia	5 days–1-year-old	66	132	35:31	Febrile UTI, bacteriuria, abnormal KUB ultrasound	X-ray voiding cystourethrography was performed using a digital fluoroscopic system immediately after the completion of echo-enhanced VUS through the same catheter left in place. The iodinated contrast medium (Iopamidol, (300 mg/ml), or Ioxitalamate, (350 mg/ml), was diluted with normal saline at body temperature, reaching an iodine concentration in solution between 85 and 105 mg of iodine in 1 ml of solution in a ratio of approximately 1:3. The contrast solution was dripped into the bladder under approximately the same hydrostatic pressure as in echo-enhanced VUS. To reduce the radiation intermittent pulsed fluoroscopy, last-image captures and digital post-processing were used in all cases. The procedure was completed when the child finished voiding	Toshiba Applio XL US machine-specific CHI and contrast-specific harmonic software dedicated for second-generation contrast. Mechanical index: 0.06–0.10 in low-specific mode	Sonovue (concentration not mentioned), 1 ml intravesical administration	The bladder was slowly filled with saline solution kept at body temperature and under hydrostatic pressure (40–70 cm H_2O). When half of the predicted volume (bladder capacity = 10 ml/kg body weight) was filled, the US contrast agent SonoVue was administered intravesically through the catheter to evaluate the bladder and the distal parts of both ureters	1 cycle at mean duration of 15 min	Assessed, none reported
Deng et al. [18] China	21 days–10-year-old	36	72	23:13	Suspected VUR on US	VCUG contrast solution (20 ml/iodine content 370 mg/ml, mixed in sterile saline solution in a ratio of 1:1–80 ml. After the catheter is inserted, the bladder is instilled with 60–120 ml contrast solution for the study imaging. When urination phase is observed, the catheter is removed for micturition study. Contrast agent distribution observed in the ureter or renal pelvis diagnosed as reflux. The VUR is backflow graded according to the reflux grading standard	Low mechanical index (0.08), with color Doppler	Sonovue 5 ml diluent (0.2 ml/3 ml) 30–60 ml preparation in 60–120 ml infusion	60–120 ml contrast solution infused for each study	1 cycle (no mention of procedure duration)	Assessed, none reported

Table 1 (continued)

References	Population	Total number of patient	Total renoureteral unit	Sex ratio (M:F)	Indication for VUR investigation	VCUG detail	Ultrasound–harmonic imaging setting	Ultrasound contrast used	Infusion method of contrast	Micturition cycle studied	Adverse event
Wozniak et al. [19] Poland	3 months–17 years and 3 months	80	161	18:62	UTI, treated with VUR	VCUG was performed by drip infusion of the heated saline with a non-ionic contrast agent Omnipaque 300 or Iomeron 300. The methodology of the study and classification used to grade VUR were consistent with the international system of VUR radiographic grading	Not described on frequency impulse, with color Doppler, supplied with tissue harmonic imaging with subsequent 3D/4D reconstruction	Sonovue (dosage not described)	Slow infusion of contrast solution	1 cycle (no mention of procedure duration)	Not described
Wong et al. [20] Hongkong	2 months–48 months	31	62	23:8	UTI	Cyclical MCU was subsequently performed independently by another group of radiologists with fluoroscopy machine. The ultrasound contrast and saline was first drained out before instillation of radiographic contrast, suspended at the same standardized height. Two cycles of filling and voiding phases were again performed under intermittent pulsed fluoroscopy with last image-hold technique	Philips iU22 machine with contrast-specific mode. Mechanical index: 0.05–0.07 harmonic imaging software	Sonovue (concentration not mentioned), 1 ml bolus injection	Bolus injection of contrast after 1/3 of estimated bladder capacity is achieved	2 cycles at 11.13 min mean duration	Assessed, none reported
Zaki et al. [21] Malaysia	1 month–16-year-old	27	55	17:10	Antenatal Pelvicalyceal dilation, UTI, neurogenic bladder, follow for VUR treatment	MCU was performed using the digital fluoroscopy performed by radiology personnel. Based on institution's standard operating procedure using room temperature saline mixed with contrast agent (300 mg/ml) to obtain a 30% concentration and introduced into the bladder by gravity drip. VUR seen on MCU was graded according to the International Reflux Study Committee Classification	Philips iU22 machine equipped with specific contrast software. Mechanical index: 0.7	Sonovue diluted into 5 ml solution, 2.5 ml infused intravesically	Intravesical infusion after maximum bladder capacity was achieved	1 cycle (duration not mentioned)	Assessed, none reported
Fernandez-Ibieta et al. [22] Spain	2 months–13-year-old	40	80	No mention	Suspicion of VUR with PUV	VCUG performed by a single radiologist according to the clinical guidelines, and parameters as previously defined for the voiding cystourethrography	Not described	Sonovue (concentration and manner of infusion not described)	Not described in detail	Not described	Not described

Table 1 (continued)

References	Population	Total number of patient	Total reno-ureteral unit	Sex ratio (M:F)	Indication for VUR investigation	VCUG detail	Ultrasound–harmonic imaging setting	Ultrasound contrast used	Infusion method of contrast	Micturition cycle studied	Adverse event
Wozniak et al. [23] Poland	1 year–13.7-year-old	69	138	21:48	UTI, hydronephrosis	VCUG performed according to the procedural recommendations of the European Society of Paediatric Radiology and the vesicoureteral reflux was graded according to the international system	Not described on frequency impulse, with color Doppler, supplied with harmonic imaging mode and subsequent 3D/4D reconstruction	Sonovue (dosage not described)	Use of contrast with no detail described	1 cycle (30 min average duration)	Not described
Piskunowicz et al. [24] Poland	1 month–17.5-year-old	83	166	46:37	UTI, ureteral dilation, suspicion of reflux nephropathy	Ce-VUS and VCUG were performed at the same time in one cycle. The solution of contrast agents for clinical use was prepared shortly before the exam under aseptic conditions. A pre-warmed plastic bottle containing 0.9% saline was filled with iodine contrast agent, followed by 0.5 ml of SonoVue. VCUG was performed without continuous real-time fluoroscopic monitoring. VCUG reflux grading was based on International System of Radiographic Grading of VUR	Voluson E8 4–8 MHz convex and 7–12 linear probes or Aloka; 5.0–8.0 MHz convex and 8.0–12.0 MHz linear probes	0.5 ml of Sonovue	A plastic bottle containing 250 ml os saline prewarmed to 32 °C, 0.5 ml Sonovue, and 30 ml Visipaque, dripped at 80 cm level from examination table	1 cycle (duration not described)	Assessed, none reported
Ntoulia et al. [25] USA	0.1 year–17-year-old	30	62	9:21	Febrile UTI, bacteriuria, abnormal KUB	VCUG was performed using the same bladder catheter placed for ceVUS, with gravity infusion of 17.2% iothalamate meglumine and pulsed fluoroscopy. VUR was according to the International System of Radiographic Grading of VUR	Accuson S3000 and Philips Epic 7 equipped with low mechanical index contrast-specific mode. Mechanical index: 0.03–0.49	Optison, 0.2%/normal saline solution was prepared (0.2/100 ml)	Infusion by gravity at 50–60 cm level above the examination table until maximum bladder capacity was achieved	Varies, depending on whether a patient voids at low bladder volume	Assessed, none reported

SROC was plotted with an estimated AUC 0.9648 (standard error 0.0124), which considered an excellent diagnostic comparability to the reference test (Supplementary Figure 6).

Assessment of funnel plot generated with dOR and SElog(dOR) from all the included studies has shown a probable plot asymmetry suggestive of small study effect (Supplementary Figure 7). Further regression test has shown a suggestive presence of publication bias (Macaskill modification of Egger's regression $t = -3.1275$, $df = 10$, $p = 0.0107$).

Discussion

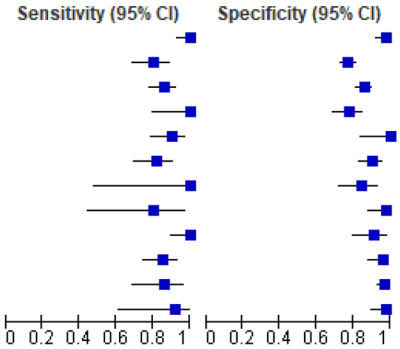
The result of our meta-analysis has indicated that based on VCUG as the reference standard, CEVUS-HI is considered to be highly accurate in detecting VUR among children. The pooled diagnostic parameters, as well as the AUC of SROC, are noted to be > 0.90, which is considered an outstanding model of diagnostic modality for predicting the condition [26]. Furthermore, studies included in this review have also reported a wide safety margin with no serious adverse events related to the use of the contrast. This was in congruence with prior reports and further justifies its application to the pediatric population [27].

Similar to the VCUG and direct radionuclide cystography (DRC), contrast-enhanced voiding urosonogram was performed by introducing intra-vesical contrast via a urethral catheter to assess the presence of retrograde urinary flow to the upper tracts [3]. While compared to the first-generation contrast (Levovist), which is off the market, the second-generation contrasts were found to have longer stability in a water solution (2 h versus 6 h), which may allow for decreased contrast volumes without compromising improved dynamic imaging, specifically when using a low mechanical index, thereby increasing its reliability [3, 14, 28].

However, unlike VCUG, contrast-enhanced voiding urosonogram is highly operator dependent requiring great proficiency and expertise, and is known to provide a poor anatomic illustration [29, 30]. This limitation has been addressed in several studies with the harmonic imaging mode of ultrasound contrast setting. The use of harmonic imaging in VUS has shown an increase in the sensitivity and specificity with superior evaluation of the retrovesical space and renal pelvis, while generating an acceptable image of the microbubbles as shown by several studies comparing with conventional VUS [29]. Several studies have shown that harmonic imaging for VUS can detect VUR with good accuracy by increasing contrast and spatial resolution, while reducing artifacts resulting in a better image quality [4].

Combining improved contrast (second or later generations) with harmonic imaging, a synergistic potential was created to improve the overall diagnostic accuracy for detecting VUR [4, 6]. The result of our meta-analysis was able to show that CEVUS-HI has optimal diagnostic accuracy in detecting VUR with high likelihood ratios as well as dOR. Furthermore, it allows for the real-time assessment of voiding dynamics with the simultaneous evaluation of upper tracts and renal parenchyma prior to more invasive and radiation containing procedures [6].

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Ascenti 2004	49	3	0	108	1.00 [0.93, 1.00]	0.97 [0.92, 0.99]
Papadopoulou 2009	57	90	14	302	0.80 [0.69, 0.89]	0.77 [0.73, 0.81]
Kis 2010	89	37	14	226	0.86 [0.78, 0.92]	0.86 [0.81, 0.90]
Kljucevsek 2012	16	26	0	90	1.00 [0.79, 1.00]	0.78 [0.69, 0.85]
Deng 2013	46	0	5	21	0.90 [0.79, 0.97]	1.00 [0.84, 1.00]
Wozniak 2013	49	10	11	91	0.82 [0.70, 0.90]	0.90 [0.83, 0.95]
Wong 2014	5	9	0	48	1.00 [0.48, 1.00]	0.84 [0.72, 0.93]
Zaki 2015	8	1	2	44	0.80 [0.44, 0.97]	0.98 [0.88, 1.00]
Fernandez-Ibieta 2016	34	4	0	42	1.00 [0.90, 1.00]	0.91 [0.79, 0.98]
Wozniak 2016	58	3	10	67	0.85 [0.75, 0.93]	0.96 [0.88, 0.99]
Piskunowicz 2016	25	4	4	133	0.86 [0.68, 0.96]	0.97 [0.93, 0.99]
Ntoulia 2017	11	1	1	49	0.92 [0.62, 1.00]	0.98 [0.89, 1.00]



Diagnostic Accuracy Parameters	Pooled with bivariate mixed effect regression model	95% Confidence Intervals
Sensitivity	90.43	90.36- 90.50
Specificity	92.82	92.76- 92.87
Positive Likelihood Ratio	12.59	12.49- 12.68
Negative Likelihood Ratio	0.103	0.102- 0.104
Diagnostic Odds ratio	122.12	120.75- 123.49

Fig. 1 The overall pooled diagnostic accuracy parameters (forest plot for sensitivity and specificity with tabulated all diagnostic accuracy parameters) generated using bivariate mixed-effects regression model for CEVUS-HI based on VCUG as reference (extrapolated numbers as renal units). *TP* true positive, *FP* false positive, *FN* false negative, *TN* true negative, *CI* confidence intervals

Our study performs a diagnostic meta-analysis appropriately according to the Cochrane Collaboration recommendation and reported according to the PRISMA-DTA [7, 8]. Furthermore, we are able to specifically assess the diagnostic accuracy of CEVUS that is attributable to the specific use of second or later generations of contrast with the harmonic imaging mode. However, despite the sensitive search strategy employed and attempt to identify unpublished studies, only a few studies were available for quantitative assessment. Publication bias was also likely, given that the available studies were reported from large centers with CEVUS and required expertise. Furthermore, the included comparative studies in this meta-analysis were found to have low to high risk of bias and a significant heterogeneity with high inter-study variability. Particularly, there are some technical and methodological differences between the studies while performing CEVUS-HI, which may affect the assessment of the diagnostic accuracy. Furthermore, the overall 26% (low) detection rate of VUR by standard reference VCUG in our pooled analysis, could be due to varied and unspecific indications for a VCUG among the included studies, which also contributes to the heterogeneity in the pooled diagnostic estimates. Despite the fact that meta-regression was not able to identify a specific source of heterogeneity nor likelihood of threshold effect to perform a subgroup analysis, we used the bivariate regression model. This analytical approach appropriately mitigates any possible interaction of the study indices or covariates with the accuracy parameter. Therefore, the generated SROC with AUC is likely to illustrate a better methodical perspective on the diagnostic accuracy of the CEVUS-HI with second-generation contrast [7, 13].

Overall based on the low–moderate quality of evidence generated from our meta-analysis, the use of CEVUS-HI as an alternative primary diagnostic modality to detect VUR cannot be strongly recommended. However, our study has an important contribution to the literature in summarizing the diagnostic parameters of CEVUS-HI and gives vital insight to clinicians who want to consider this as an alternative option for evaluation of children with VUR. It is particularly useful if a large volume center with the appropriate expertise would want to invest in state-of-the-art technology and increase their armamentarium of diagnostic studies. With the availability of newer contrast materials and more sophisticated ultrasound machines, further exploration of the adjunctive and synergistic potentials with contrast-enhanced voiding urosonogram for detecting VUR is recommended.

Conclusion

Our meta-analysis based on low–moderate quality of evidence has shown that CEVUS-HI, when compared to VCUG, has an acceptable diagnostic accuracy in detecting VUR among children. With its good safety profile and lack of ionizing radiation, CEVUS-HI may be considered as an alternative to VCUG. This diagnostic modality is particularly optimal for highly specialized centers with expertise on the approach.

Author contributions MEC: Protocol/project development, data collection or management, data analysis, manuscript writing/editing. JSM: Protocol/project development, data collection or management, data analysis, manuscript writing/editing. JMM: Data collection, manuscript editing/revision. JSD: Data analysis, manuscript writing/editing. OG: Protocol/project development, data collection or management, data analysis.

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Compliance with ethical standards

Conflict of interest All authors have nothing to disclose.

Ethics approval The study was approved and registered in our institutional research board as exempt for review.

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