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Systematic review of the performance of non-invasive tests in diagnosing bladder outlet obstruction in men with lower urinary tract symptoms

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Abstract

Context:
Several non-invasive tests have been developed for the diagnosis of bladder outlet obstruction (BOO) in men to avoid the burden and morbidity associated with invasive urodynamics. The diagnostic accuracy of these tests, however, remain uncertain.

Objective:
To systematically review the available evidence regarding the diagnostic accuracy of non-invasive tests in diagnosing BOO in men with lower urinary tract symptoms (LUTS) using the pressure-flow study as a reference standard.

Evidence acquisition:
The EMBASE, MEDLINE, Cochrane Database of Systematic Reviews, Cochrane Central, Google Scholar, and WHO International Clinical Trials Registry Platform Search Portal databases were searched up to May 18th 2016. All studies reporting the diagnostic accuracy of non-invasive tests for BOO or DUA in men with LUTS compared to pressure-flow studies were included. Two reviewers independently screened all articles, searched the reference lists of retrieved articles, and performed the data extraction. The quality of evidence and risk of bias was assessed using the QUADAS-2 tool.

Evidence synthesis:
The search yielded 2,774 potentially relevant reports. After screening titles and abstracts 53 reports were retrieved for full-text screening, of which 42 (recruiting a total of 4444 patients) proved eligible. Overall, the results were predominantly based on findings from non-randomised experimental studies and, within the limits of such study designs, the quality of evidence was typically moderate across the literature. Differences in the non-invasive test BOO threshold values and variations in the urodynamic definition of BOO between studies limited the comparability of the data. The detrusor wall thickness (median sensitivity 82%, specificity 92%), near-infrared spectroscopy (median sensitivity 85%, specificity 87%), and penile cuff test (median sensitivity 88%, specificity 75%) were all found to have high sensitivity and specificity in diagnosing BOO. Uroflowmetry with a maximum flow rate of less than 10ml/s was reported to have a lower median sensitivity and specificity of 68% and 70%, respectively. Intravesical prostatic protrusion of more than 10mm was reported to have a similar diagnostic accuracy with a median sensitivity and specificity of 68% and 75%.

Conclusions:
A number of non-invasive tests have been shown to have a high sensitivity and specificity in the diagnosis of BOO in men. However, although the majority of studies have a low overall risk of bias the available evidence is limited by heterogeneity. While several tests have shown promising results regarding the non-invasive assessment of BOO, invasive urodynamics remain the gold standard.

Patient summary:
Urodynamics is an accurate but potentially uncomfortable test for patients in diagnosing bladder problems such as obstruction. We performed a thorough and comprehensive review of the literature to

determine if there were less uncomfortable but equally effective alternatives to urodynamics for diagnosing bladder problems. We found some simple tests which appear promising although they were not as accurate. Further research is needed before these tests are routinely used in place of urodynamics

1 Introduction

Lower urinary tract symptoms (LUTS) are prevalent and bothersome in men and women of all ages. Determining whether these symptoms are due to bladder outflow obstruction (BOO) is important in determining the optimal management (1). Indeed, the success rate from surgical procedures, such as transurethral resection of the prostate, is presumed to be superior in patients with urodynamically documented BOO. However, it is not possible to reliably diagnose BOO based on clinical symptoms alone, and the gold standard for diagnosis is by urodynamic assessment with a pressure-flow study. However, this is an invasive test with risks of bothersome urinary symptoms, haematuria and urinary tract infection. Furthermore, it can be unpleasant, with considerable rates of anxiety and embarrassment (2). It also requires dedicated equipment and specific expertise, and is expensive. Consequently, a number of non-invasive tests have been described to replace the pressure-flow study in diagnosing BOO in men with LUTS. The objective of this systematic review is to determine the diagnostic accuracy of non-invasive tests in diagnosing BOO in men with LUTS with reference to the gold standard, invasive urodynamics.

2. Evidence acquisition

We used standard methods recommended by the Cochrane Methods Group for the Systematic Review of Screening and Diagnostic Tests (3), Preferred Reporting Items for Systematic Reviews (PRISMA), and Standards for Reporting Diagnostic Accuracy Studies (STARD) (4). The study protocol was published on PROSPERO (CRD42015019412).

2.1 Search strategy

An experienced research librarian (CY) collaborated in planning the search strategy. The EMBASE, MEDLINE, Cochrane Database of Systematic Reviews, Cochrane Central (Cochrane HTA, DARE, HEED), Google Scholar, and WHO international Clinical Trials Registry Platform Search Portal databases were searched up to May 18th 2016. Only English language articles were included and the detailed search strategy is described in Appendix 1. Additional sources of articles included the reference lists of included studies and clinical content experts (European Association of Urology Male LUTS Guideline Panel). Two reviewers (SM and RU) screened all abstracts and full-text articles independently. Disagreement was resolved by discussion, and where no agreement was reached, a third independent party acted as an arbiter (AKN).

2.2 Types of study design included

All types of studies (including at least 10 participants) assessing the diagnostic accuracy of non-invasive tests using invasive urodynamics as a reference standard were eligible.

2.3 Types of participant included

Eligible study populations recruited adult men (≥18 years) with LUTS (as defined by the study authors). Studies where the proportion of men with either neurological disease or urethral stricture was higher than 10% were excluded.

2.4 Types of intervention included

The following non-invasive tests (i.e. index tests) were eligible for inclusion. A detailed description of each index test is included in Appendix 2.

1. Prostate volume/height
2. Intravesical prostate protrusion (IPP)
3. Detrusor/bladder wall thickness measured on transabdominal ultrasound (DWT/BWT)
4. Ultrasound-estimated bladder weight (UEBW)
5. Doppler ultrasound
6. Near-infrared spectroscopy (NIRS)
7. Uroflowmetry
8. Penile cuff test (PCT)
9. External condom catheter method

2.5 Outcome measures

The primary outcome measures for diagnostic accuracy for predicting BOO were sensitivity, specificity, positive predictive value and negative predictive value. Secondary outcome measures included test reliability and reproducibility, adverse events, patient satisfaction, and cost effectiveness as defined by the trial authors, if reported.

2.6 Assessment of risk of bias

The risk of bias (RoB) in the included studies was assessed using the QUADAS-2 tool (5). It consists of 4 domains of patient selection, index test, reference standard, and the flow of patients through the study, and timing of the index test and reference standard. RoB was assessed for each domain, and the first 3 domains were also assessed for concerns regarding applicability.

A list of the most important potential confounders for outcomes was developed *a priori* with clinical content experts (EAU Non-neurogenic Male LUTS guideline panel). The confounder assessment consisted of whether each prognostic confounder was considered and whether, if necessary, the confounder was controlled for in the analysis. The potential confounding factors assessed were: (1) whether indices for pressure flow study were determined automatically or manually; (2) whether the quality of urodynamic study adhered to contemporaneous quality standards (i.e. International

Continence Society standards for studies from 2002 onwards; for studies pre-2002, judgement was made by the reviewer and panel member).

2.7 Data analysis

Due to the expected heterogeneity in the definitions, thresholds and technical variations of the included index tests, a qualitative (i.e. narrative) synthesis of all included studies was planned. For studies with multiple publications, only the most up-to-date or complete data for each outcome was analysed.

Subgroup analyses were planned for the following groups, if data were available: High vs. low prevalence of BPE, men with a high prevalence of detrusor underactivity (DUA), men with storage versus voiding LUTS, severity of LUTS, men with previous prostate surgery, men treated with medical therapy for storage and/or voiding LUTS, and risk factors for BPE (PSA, Prostate volume, post-void residual.

For each study, the elements of diagnostic accuracy were determined by way of a two-by-two contingency table consisting of true positive (TP), false positive (FP), false negative (FN) and true negative (TN) based on data reported by authors. If there was discrepancy between the observed data (i.e. TP, FP, FN and TN) and derived data (i.e. sensitivity, specificity, positive predictive value and negative predictive value), the observed data took priority, and diagnostic accuracy elements were calculated from the observed data as reported by authors. In addition, descriptive statistics including median and interquartile range, and range, were provided for all diagnostic accuracy elements for each type of index test considered as a whole to provide a summary measure across studies. Sensitivity analysis was planned for each type of index test using the most commonly used threshold values relevant to each test only.

3 Evidence synthesis

3.1 Quantity of evidence identified

The study selection process is outlined in Fig. 1. A total of 42 studies were eligible for inclusion: 41 non-randomised experimental studies and 1 retrospective comparative study (6-47).

3.2 Characteristics of included studies

The baseline characteristics of all 42 included studies are shown in Table 1. A total of 4,444 patients were recruited.

3.3 Risk of bias assessment

The summary of methodological quality and RoB assessments is shown in Fig. 2. The majority of studies had a low RoB in terms of applicability, with most studies including men that are representative of those that would be expected to undergo this test in routine practice. The study by Botkor-Rasmussen included a larger proportion of asymptomatic or minimally-symptomatic men

compared to the other studies, and Sullivan et al. included some normal volunteers, which could therefore affect the applicability of the diagnostic test accuracy results obtained (12, 44). Hirayama et al. included only men with small prostates (<20ml) which would not be a representative sample of those that would receive the test in clinical practice, and Kuo et al. used a definition of BOO on urodynamics (PdetQmax >50 cmH_2O) that is not widely accepted and therefore may affect the accuracy of the results (21, 27).

The principal source of bias across studies related to the reporting of the reference standard. Although the ICS nomogram is now widely accepted to define BOO on voiding cystometry, a number of studies used different definitions of BOO which may affect the diagnostic accuracy results obtained. Furthermore, some studies classified both equivocal and non-obstructed patients into the same non-obstructed group which may introduce an element of bias into the overall results (6). In addition to this, blinding to the index test and reference standard was either not clearly discussed or was not performed in a number of studies, again accounting for an unclear or high RoB in data interpretation across studies. In the studies assessing NIRS, the index test and reference standard had to be undertaken simultaneously and so this introduces a RoB with the same investigator analysing the results of both tests at the same time.

The overall RoB across most domains was generally low across most studies, although there was significant heterogeneity of definitions of thresholds, index tests and reference tests.

3.4 Narrative synthesis of results

3.4.1 Diagnostic accuracy results

The individual results for each study, organised according to the index test being assessed, are shown in Table 2. The overall results for each type of index test considered are available in Table 3. It was not possible to perform subgroup analyses because of lack of data.

3.4.1.1 Penile cuff test

Seven studies investigated the diagnostic accuracy of the penile cuff test. Overall, diagnostic accuracy was high with a median sensitivity and specificity of 88% and 70%, respectively. There was a low risk of bias across most studies but significant heterogeneity in the threshold values used to diagnose BOO, with 3 studies using the nomogram developed by Griffiths et al. (11, 18, 22), two using different nomograms (32, 42), and two using a penile urethral compression-release (PCR) index of either 160% or 100% (20, 44). As a result, it is impossible to reliably pool the results of these studies.

3.4.1.2 Uroflowmetry

Uroflowmetry was assessed in a total of 2,580 patients across 16 studies. Thirteen studies used a cut-off value of 10ml/s to diagnose BOO and reported a median sensitivity and specificity of 68.3% and 70.5%, respectively, with a PPV and NPV of 74.3% and 68% (7, 12, 13, 15, 16, 18, 20, 21, 26, 30, 33, 34, 38, 40, 41). However, studies varied considerably in their choice of defining variable and cut-off values. The range of sensitivity and specificity values across studies was so wide that no conclusions can be drawn. As would be expected, lowering the cut-off value for Qmax seemed to increase sensitivity at the expense of specificity and vice-versa. But baseline symptom severity also acts as a significant confounder which we are unable to control for with the available data. Overall the

diagnostic accuracy of uroflowmetry in diagnosing BOO appears to be relatively limited compared with the other index tests.

3.4.1.3 Detrusor or bladder wall thickness (DWT/BWT)

DWT was studied in 848 patients across 8 studies (6, 8, 16, 17, 24, 31, 33, 34), 5 of which used a cut-off of 2mm to define BOO with a high median sensitivity and specificity of 82.7% and 92.6%, respectively, with a PPV and NPV of 90.5% and 85%, respectively. Furthermore, a well-conducted exploratory study reported a cut-off value of 2.9mm as having the best diagnostic value, with a specificity of 100%. Altered DWT and BWT may have a multifactorial basis, and further assessments in well-designed statistically-powered trials are needed to assess wider application in clinical service delivery.

3.4.1.4 Bladder weight (UEBW)

UEBW was only assessed in 2 studies, both utilising different threshold values to define BOO, and both finding a wide variation in diagnostic accuracy (19, 25). Therefore, little inference can be made based on the available data on bladder weight.

3.4.1.5 External condom method

The external condom catheter method was assessed in a single study reporting that up to 73% of patients could be correctly diagnosed with the external condom catheter technique (37). However, from the limited data available it appears that test failure, for various reasons, is a limiting factor.

3.4.1.6 Intravesical prostatic protrusion (IPP)

IPP was studied in a total of 1,013 patients across 10 studies (6, 8, 9, 13, 15, 17, 23, 28, 36, 39). Five studies used a cut-off of 10mm to define BOO and overall reported a similar diagnostic accuracy to uroflowmetry alone with a median sensitivity and specificity of 67.8% and 74.8%, with a PPV and NPV of 73.8% and 69.3%. However, threshold values varied, making interpretation difficult.

3.4.1.7 Doppler ultrasound

Two studies evaluated the role of Doppler ultrasound, one assessing detrusor blood flow and the other assessing urinary flow velocity (10, 35). The small patient numbers render the results on Doppler ultrasound difficult to interpret with any degree of certainty.

3.4.1.8 Prostate volume and height

Four studies assessed prostate volume or height, and various threshold values were employed, but all of them reported low diagnostic accuracy (16, 17, 28, 45).

3.4.1.9 Near-infrared spectroscopy (NIRS)

NIRS was assessed in 5 studies, 3 of which used the NIRS algorithm to define BOO (14, 29, 43, 46, 47). Overall diagnostic accuracy was relatively high with a median sensitivity and specificity of 85.7% and 87.5%, respectively. The one study using a mathematical modelling and regression tree algorithm showed the highest diagnostic accuracy (43).

3.4.2 Results for secondary outcomes

Secondary outcomes were not addressed due to the lack of data suitable for a critical analysis.

3.5 Discussion

3.5.1 Principal findings

A total of 42 studies recruiting a total of 4,444 patients were eligible for inclusion in this SR, which assessed the diagnostic accuracy of 9 non-invasive tests. There were significant variations among studies investigating the same test, both in terms of the threshold value used to define BOO on the non-invasive test as well as the nomograms used to diagnose BOO on invasive urodynamics. For studies reporting on most commonly used thresholds to define BOO, the penile cuff test using the Griffiths nomogram, DWT > 2mm and the NIRS algorithm had the highest median sensitivities ranging from 82-85.7%. These three tests also had the highest median NPV's of 84-89%. The highest median PPV's were reported for DWT >2mm and the NIRS algorithm, at approximately 90%. The diagnostic accuracy for IPP >10mm was similar to that for a Qmax <10ml/s on free flow rate testing. The studies on IPP also appeared to show that specificity increased with increasing IPSS score, a confounder that would be controlled for in a good prospective trial. The diagnostic ability of the external condom catheter seems promising in the only study included, but this data requires further validation in future studies.

Although the overall RoB was low across many domains for the majority of studies, in many studies, the index test and reference standard were performed unblinded, and in some studies the two tests were performed simultaneously by the same investigator who also analysed the results obtained. This could have potentially biased the interpretation of the findings and final conclusions reached.

3.5.2 Implications for clinical practice

Pressure-flow studies for the evaluation of men with LUTS are often not performed for practical reasons. Several non-invasive techniques have therefore been developed and appear promising in the assessment of men with LUTS. From the evidence reviewed in this paper, the penile cuff test, DWT, UEBW and NIRS have shown the greatest diagnostic accuracy although further validation in studies with more stringent methodological standards are required before they can replace invasive urodynamics. Furthermore, there are a number of factors that need to be considered when discussing generalisability and delivery costs of these tests. The penile cuff test may cause discomfort or urethral bleeding, although this has been reported in only 2% of patients, and technical difficulties have been reported to result in exclusion rates of 23% to 46% (48, 49). Similarly, the external condom method may also cause discomfort and results may be affected by low flow rates, low voided volumes, and abdominal straining (37). Measurement of DWT and UEBW require specific training and there is a risk of observer error, and NIRS requires specialised equipment. Doppler ultrasound urodynamics suffers from the same limitations of observer error and requires specialised equipment to perform. It is clear that these techniques, either alone or in combination, may be used to aid decision-making and counselling when evaluating men with LUTS in daily clinical practice, especially if invasive urodynamics are unavailable or contra-indicated. However, the quality of the current data is

insufficient to recommend the routine use of any non-invasive test over pressure-flow studies in diagnosing BOO in men with LUTS.

3.5.3 How the review compares with previous reviews/guidelines

A number of studies reviewing the evidence for various non-invasive urodynamic tests have been published in recent years (50-57). All reviews have reported similar findings to the present review, reporting that some non-invasive tests appear promising, especially in combination, but further investigation is required before they can replace invasive urodynamics. Importantly, however, the methodology in these reviews differ significantly from the present SR. Primarily, this SR is based on strict inclusion and exclusion criteria with input from a multidisciplinary expert panel to inform the review question. The robust methods used to synthesise the evidence and analyse the data are the principal strengths of this study and therefore provide a more accurate evaluation of the available evidence compared to the other reviews.

3.5.4 Future research

This review has demonstrated that several non-invasive tests seem promising in assessing men with BOO. However, we have highlighted the limitations of the current evidence base in terms of heterogeneity of definitions and threshold values used, and therefore larger studies with more stringent methodological standards are required in order to better assess their role in the evaluation of men with LUTS. The limitations of existing individual tests have led many investigators to assess the role of a combination of tests in improving the diagnostic accuracy for BOO. Although not covered in this SR, the role of combining tests is a promising area that requires further assessment.

3.5.5 Strengths and Limitations

The strengths of this review are the systematic, transparent, and effective approach taken to examine the evidence base, including the use of Cochrane review methodology, the assessment of RoB using QUADAS-2, and adherence to PRISMA and STARD guidelines. The clinical question was prioritised by a multidisciplinary panel of clinical experts, methodologists and patient representative (EAU Non-neurogenic Male LUTS Guideline Panel), and the work was undertaken as part of the panel's clinical practice guideline update for 2016. In addition, the review elements including characteristics of participants, index and reference tests, definitions and thresholds were developed *a priori* in conjunction with the panel. The search strategy was complemented by additional sources for potentially important articles, including reference lists of included studies and studies identified by the expert panel. This approach ensured a comprehensive review of the literature while maintaining methodological rigour and enabled the authors to put into clinical context the relevance and implications of the review findings. Moreover, the vast majority of studies were prospective in nature, with well-defined index and reference tests, and the overall RoB was generally low across studies. The primary limitation was the large heterogeneity among studies, with regard to definitions of index tests and reference standards. Furthermore, due to lack of data we were unable to perform any subgroup analyses. Another limitation is the basic assumption that invasive urodynamics is a definitive diagnostic investigation for BOO in men. It is known that results of invasive urodynamics and the nomograms based upon pressure-flow studies can have significant inter and intra-investigator variability as well as test-retest variation (58, 59). However, in the absence of a more accurate gold-standard, all studies on these diagnostic tests will continue to be compared to invasive urodynamics.

4 Conclusion

This study has systematically reviewed the evidence assessing the diagnostic accuracy of non-invasive tests in diagnosing BOO in men with LUTS using effective methods of evidence acquisition and synthesis, with input from a multidisciplinary expert panel to inform the review question and review elements. The findings and clinical relevance were interpreted with appropriate clinical context provided by the expert panel. Overall, a number of non-invasive tests appear promising with a low RoB across most domains for the great majority of studies. Limitations of the current evidence base include heterogeneity of definitions and thresholds in regard to index tests and reference standards, and therefore this review has highlighted the need for larger prospective studies with better methodological quality. In spite of these limitations, the findings from this review can help to provide clinical guidance on the accuracy of these tests in daily practice. Therefore, while several tests have shown promising results regarding the non-invasive assessment of BOO, pressure-flow study remains the gold standard test in determining BOO.

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Disclosures:

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: Tikkinen declares no conflicts of interest.

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Appendix 1: Literature Search Strategy

The following databases were searched using the provided search strategy:

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <April 2016>, EBM Reviews - Cochrane Database of Systematic Reviews <2005 to May 18, 2016>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>, Embase <1974 to 2016 May 18>

Search Strategy:

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1 exp bladder neck stenosis/ or exp Urinary Bladder Neck Obstruction/

2 exp bladder obstruction/

3 (bladder adj2 (neck sclerosis or outflow obstruction or outlet obstruction or obstructed voiding)).tw,kw.

4 exp prostate hypertrophy/ or exp Prostatic Hyperplasia/

5 (benign prostatic hyperplasia or BPH or benign prostatic obstruction or BPO or benign prostatic enlargement or BPE or BOO or prostate hypertrophy).tw,kw.

6 (((detrusor or bladder) adj2 (underactivit* or failure or acontractile or hypocontract*)) or DUA).tw,kw.

7 or/1-6

8 (pressure adj2 flow).tw,kw.
9 exp urodynamics/
10 exp cystometry/ or flow Cytometry/
11 (urodynamic* or cystometrogram or cystometr* or cystometrography or cystomanometry).tw,kw.
12 exp bladder pressure/
13 (detrusor pressure or bladder pressure).tw,kw.
14 or/8-13
15 exp non invasive measurement/
16 (non invasive adj2 (test or measurement)).tw.
17 (videourodynamics or Video urodynamics).tw,kw.
18 (uroflowmetry or Urine flowmetry or urine flow measurement or intraureteral flow measurement).tw.
19 ((Penile cuff or UroCuff or free flow rate) adj3 (test or study)).tw.
20 (Bladder wall thickness or detrusor wall thickness or Bladder weight).tw.
21 (Condom method or Presumed circle area ratio or Intravesical prostatic protrusion).tw.
22 exp uroflowmetry/
23 exp urine flow rate/
24 or/15-23
25 7 and 14
26 7 and 24
27 25 or 26
28 exp Lower Urinary Tract Symptoms/
29 (((lower urinary tract or bladder or urethra* or LUT) adj3 (symptom* or complain*)) or LUTS).tw.
30 28 or 29
31 27 and 30
32 (exp animals/ not humans/) or ((rats or mice or mouse or cats or dogs or in vitro or cell lines) not (human* or men or women)).ti.
33 31 not 32
34 (children/ not adult/) or ((children or pediatric* or paediatric*) not (aged or adult* or men or women)).ti.
35 33 not 34
36 women/ not (men/ or (men or male).mp.)
37 35 not 36
38 (case report/ or case reports/) not (case series or cases).ti,ab.
39 37 not 38
40 note/ or editorial/ or Comment/ or news/
41 39 not 40
42 remove duplicates from 41

Appendix 2: Detailed description of non-invasive tests included in this review

1. Penile cuff test

This test involves the placement of a pneumatic cuff around the penile shaft which is inflated on voiding, thereby interrupting flow. The pressure of the resultant fluid column in the urethra is estimated to be intravesical pressure and can be used as a measure of bladder contractility (18).

2. Uroflowmetry

The patient is asked to urinate into a container which measures the rate and volume of urine voided, and the post-void residual urine volume is then measured with ultrasound. This enables the calculation of the maximum flow rate (Qmax) in ml/s and the flow time, as well as allowing assessment of the patter of flow (60).

3. Detrusor/bladder wall thickness measured on transabdominal ultrasound

These tests involve measuring the thickness of the detrusor muscle or entire bladder wall using transabdominal ultrasound. They are based on the findings from animal models and morphological studies that BOO results in detrusor muscle hypertrophy (61, 62), leading to increased BWT and DWT.

4. Bladder weight

The measurement of ultrasound-estimated bladder weight (UEBW) is based on the same principle as that for BWT or DWT, with bladder weight acting as a measure of detrusor hypertrophy (19).

5. External condom catheter method

The condom method is another way by which isovolumetric bladder pressure can be measured, and is based on the same principle as the penile cuff tests. The test involves voiding through a condom catheter attached to a valve, and at maximum flow the catheter is occluded and isovolumetric pressure measured via a side-port on the valve (63, 64).

6. Intravesical prostate protrusion

The intravesical prostatic protrusion (IPP) is a transabdominal ultrasound-derived measure of prostatic configuration, based on the theory that the prostate protrudes into the bladder as it grows, and therefore leads to BOO as a result of a ball-valve effect (65).

7. Doppler ultrasound

This involves the use of Doppler ultrasound to measure detrusor blood flow or velocity of urine flow. It is based on the principle that detrusor blood flow is reduced in patients with BOO and that measuring the detrusor arterial resistive index may be able to predict BOO. Furthermore, by measuring the urinary flow velocity in different parts of the urethra, the velocity ratio can be calculated and may be used to diagnose BOO (10).

8. Prostate volume/height

This is a transabdominal ultrasound-based measurement of the prostatic configuration.

9. Near-infrared spectroscopy (NIRS)

This technique involves the measurement of changes in the concentration of oxyhaemoglobin and deoxyhaemoglobin (chromophores) in tissue. It is based on the hypothesis that BOO is associated with a reduction in detrusor blood flow and oxyheamoglobin levels due to the increased work of the detrusor muscle. Consequently, BOO would result in a downward NIRS pattern of slope changes in chromophore concentration whereas an unobstructed system would lead to an upward slope (57).

Table 1. Baseline characteristics of included studies

Author and year of publication	No. of patients	Study design	Index test			Reference standard definition of BOO
			Index test	***Threshold value***	***Blinding***	
Abdel-Aal et al. 2011	85	Non-randomised experimental	DWT IPP Combination IPP + DWT	2mm 8mm 8mm + 2mm	Yes	BOOI >40
Aganovic 2004	102	Non-randomised experimental	Uroflowmetry	10ml/s	NR	LPURR>2
						LPURR>3
						LPURR>2 + URA>29
						Qmax<15 and pDetQmax >50
Aganovic et al. (a) 2012	111	Non-randomised experimental	IPP BWT	10mm 5mm	NR	BOOI >40
Aganovic at el. (b) 2012	112	Non-randomised experimental	IPP	12mm	NR	BOOI >40
			BOON	-27.2		BOOI >40
			BOON	-27.2		URA>29
			Combination IPP + BOON	10mm, -30		BOOI >40
			BOON2	-47.4		URA>29
			BOON2	-50		URA>29
Belenky et al. 2003	29	Non-randomised experimental	Doppler Ultrasound	RI T>0.05	Yes	BOOI >40
Bianchi et al. 2014	48	Non-randomised experimental	PCT	Griffiths nomogram	No	BOOI >40
Botkor-Rasmussen et al. 1999	29	Non-randomised	Uroflowmetry	10ml/s	No	BOOI >40

		experimental				
Chia et al. 2003	200	Non-randomised experimental	Uroflowmetry IPP	10ml/s 10mm	Yes	BOOI >40
Chung et al. 2010	33	Non-randomised experimental	NIRS pattern on free flow NIRS pattern on pressure-flow studies	Downward pattern Downward pattern	No	BOOI >40
Dicuio et al. 2005	25	Non-randomised experimental	IPP	10mm	No	DAMPF score
ElSaied et al. 2013	50	Non-randomised experimental	DWT Uroflowmetry Prostate volume	2mm 10ml/s 25ml	Yes	BOOI >40
Franco et al. 2010	100	Non-randomised experimental	IPP DWT Prostate height Prostate volume	12mm 6mm 40mm 38ml	Yes	BOOI >40
Griffiths et al. 2005	144	Non-randomised experimental	PCT Uroflowmetry	Griffiths nomogram 10ml/s	No	BOOI >40
Han et al. 2011	193	Non-randomised experimental	Corrected UEBW (UEBW/BSA)	27.86gm	NR	BOOI >40
Harding et al. 2004	101	Non-randomised experimental	PCT Uroflowmetry	PCR index 160% 10ml/s	Yes	BOOI >40
Hirayama et al. 2002	36	Non-randomised experimental	Uroflowmetry	10ml/s	NR	BOOI >40
Kazemeyni et al.	51	Non-	PCT	Griffiths	NR	BOOI >40

2015		randomised experimental		nomogram		
Keqin et al. 2007	206	Retrospective	IPP	8.5	NR	BOOI >40
Kessler et al. 2006	102	Non-randomised experimental	DWT	1.5mm 2mm 2.5mm 2.9mm	No	BOOI >40
Kojima et al. 1997	65	Non-randomised experimental	UEBW	35gm	No	BOOI >40
Ku et al. 2009	212	Non-randomised experimental	Uroflowmetry Residual fraction	10ml/s 12ml/s 15ml/s 10% 20% 30%	No	BOOI >40
Kuo et al. 1999	324	Non-randomised experimental	Uroflowmetry	10ml/s	No	Pdet Qmax >50 used to define BOO
Lim et al. 2006	95	Non-randomised experimental	IPP Prostate volume	10mm 40ml	NR	BOOI >40
Macnab et al. 2008	55	Non-randomised experimental	NIRS	NIRS algorithm	No	Not defined
Madersbacher et al. 1997	253	Non-randomised experimental	Uroflowmetry	5ml/s	No	LinPURR>2
Manieri et al. 1998	170	Non-randomised	BWT	5mm	Yes	URA>29

		experimental				
Matulewicz et al. 2015	19	Non-randomised experimental	PCT	Modified ICS nomogram	No	NR
Oelke et al. 2002	70	Non-randomised experimental	DWT Uroflowmetry	2mm 15ml/s	NR	CHESS
Oelke et al. 2007	160	Non-randomised experimental	DWT	2mm	Yes	BOOI >40
			Uroflowmetry	10ml/s		
			Uroflowmetry	15ml/s		
Ozawa et al. 2000	22	Non-randomised experimental	Doppler Ultrasound	VR >1.6	NR	BOOI >40
Pascual et al. 2011	39	Non-randomised experimental	MLL	10.5mm	No	BOOI >40
Pel et al. 2002	56	Non-randomised experimental	External condom catheter	Qmax/PextMax	No	BOOI >40
Poulsen et al. 1994	153	Non-randomised experimental	Uroflowmetry	10ml/s	No	BOOI >40
Reis et al. 2008	42	Non-randomised experimental	IPP	10mm	Yes	BOOI >40
				5mm		
Reynard et al. 1996	148	Non-randomised experimental	Uroflowmetry Uroflowmetry - multiple	10ml/s 1st void 10ml/s 4th void	No	BOOI >40
Reynard et al. 1998	897	Non-randomised experimental	Uroflowmetry	10ml/s	No	Shafer nomogram
Salinas et al.	93	Non-	PCT	Nomogram	Yes	BOOI >40

2003		randomised experimental		described		
Stothers et al. 2010	64	Non-randomised experimental	NIRS	CART model	No	BOOI >40
Sullivan et al. 2000	90	Non-randomised experimental	Penile compression release	PCR 100%	NR	outlet obstruction was defined as a voiding profilometry gradient across the bladder neck and prostatic urethra of >5 cm H2O in the absence of distal obstruction.
Watanabe et al. 2002	51	Non-randomised experimental	Prostate volume and H:W	30ml and 0.8	No	LinPURR ≥3
Yurt et al. 2012	53	Non-randomised experimental	NIRS	NIRS algorithm	No	BOOI >40
Zhang et al. 2013	87	Non-randomised experimental	NIRS	NIRS algorithm	Yes	BOOI >40
			uroflowmetry + PVR	10ml/s and 100ml		

Table 1: Baseline characteristics of included studies

Key: *BOOI* = Bladder outflow obstruction index, *BOON* = bladder outflow obstruction number, *BWT* = bladder wall thickness, *CART* = classification and regression tree, *DWT* = detrusor wall thickness, *DAMPF* = detrusor-adjusted mean PURR factor, *LPURR* = linear passive urethral resistance relation, *NIRS* = near-infrared spectroscopy, *NR* = not reported, *NPV* = negative predictive value, *PCR* = penile compression ratio, *PPV* = positive predictive value, *RI* = resistive index, *UEBW* = ultrasound-estimated bladder weight, *URA* = urethral resistance algorithm, *VR* = velocity ratio

Table 2. Summary of results for all index tests

Key: *BOOI* = Bladder outflow obstruction index, *BWT* = bladder wall thickness, *CART* = classification and regression tree, *DWT* = detrusor wall thickness, *DAMPF* = detrusor-adjusted mean PURR = factor, *DAN-PSS* = Danish prostatic symptom score, *IPSS* = International prostate symptom score, *LPURR* = linear passive urethral resistance relation, *NIRS* = near-infrared spectroscopy, *NR* = not reported, *NPV* = negative predictive value, *PCR* = penile compression ratio, *PPV* = positive predictive value, *RI* = resistive index, *UEBW* = ultrasound-estimated bladder weight, *URA* = urethral resistance algorithm, *VR* = velocity ratio

Penile Cuff test

Study	Threshold value	Reference standard definition of BOO	Mean age (range)	Mean IPSS (range)	Prevalence of BOO (%)	Sensitivity	Specificity	PPV	NPV
Bianchi et al. 2014	Griffiths nomogram	BOOI >40	61.5	NR	44	100	63	67.7	100
Griffiths et al. 2005	Griffiths nomogram	BOOI >40	NR	NR	39	64	81	68	78
Kazemeyni et al. 2015	Griffiths nomogram	BOOI>40	66.5	NR	35	88.89	75.7	66.7	93
Harding et al. 2004	PCR index 160%	BOOI >40	63 (20-88)	NR	28	78	84	69	NR
Matulewicz et al. 2015	Modified ICS nomogram	NR	NR	16 (6-30)	NR	75	66	92	NR
Salinas et al. 2003	Nomogram described in paper	BOOI >40	54.1	NR	28	100	55.6	71.4	100
Sullivan et al. 2000	PCR 100%	outlet obstruction was defined as a voiding profilometry gradient across the bladder neck and prostatic urethra of >5 cm H2O in the absence of distal obstruction.	NR	NR	48	90.7	70.2	73.6	89.2

Uroflowmetry

Study	Threshold value	Reference standard definition of BOO	Mean age, yr	Mean IPSS (range)	Prevalence of BOO (%)	Sensitivity	Specificity	PPV	NPV
Aganovic 2004	10ml/s	LPURR>2	64.68	14.48	63	63	88	94	42
		LPURR>3				72	69	69	72
		LPURR>2 + URA>29				72	92	94	68
		Qmax<15 and pDetQmax >50				67	45	50	63
Botkor-Rasmussen et al. 1999	10ml/s	BOOI >40	Median 66 (51-85)	DAN-PSS 4	52	33	100	100	58
Chia et al. 2003	10ml/s	BOOI >40	64.6 (50-94)	20.3	63	90	48	74	75
Dicuio et al. 2005	10ml/s	DAMPF score	67.9 (47-86)	22.4 (6 - 35)	64	NR	NR	100	NR
ElSaied et al. 2013	10ml/s	BOOI >40	61.7 (53-76)	13.4 (4 - 22)	46	100	37	57.5	100
Griffiths et al. 2005	10ml/s	BOOI >40	NR	NR	39	59	89	77	77
Harding et al. 2004	10ml/s	BOOI >40	63 (20-88)	NR	28	81	64	51	
Hirayama et al. 2002	10ml/s	BOOI >40	67.7 (50-83)	17.1 (9 - 33)	60	NR	NR	65	NR
Ku et al. 2009	10ml/s	BOOI >40	Median 68 (44-89	18.1 (no BOO), 19.7 (BOO)	27	57.9	65.8	38.4	81
	12ml/s					77.2	54.2	38.3	86.6
	15ml/s					94.7	27.7	32.5	93.5
Madersbacher et al. 1997	5ml/s	LinPURR>2	66.5 (53-81)	16	53	16	96	85.1	46.9

Oelke et al. 2002	15ml/s	CHESS	63 (42-82)	14.4 (2 - 29)	47	100	25	55	100
Oelke et al. 2007	15ml/s	BOOI >40	62 (40-89) (Median)	15 (2 - 30) (Median)	47	99	39	59	97
	10ml/s					68	73	69	72
Poulsen et al. 1994	10ml/s	BOOI >40	68 (32-90)	DAN-PSS 10 (No BOO), 11 (BOO)	65	68.7	57.4	74.7	50
	15ml/s					89.9	31.5	70.6	62.9
Reynard et al. 1998	10ml/s	Shafer nomogram	66.5 (45-88)	NR	60	47	70	70	46.5
	15ml/s					82	38	67	57.6
Reynard et al. 1996	10ml/s 1st void	BOOI >40	NR	NR	61	71	71	79	61
	10ml/s 4th void					29	96	93	47

Detrusor and bladder wall thickness

Study	Index test	Threshold value	Reference standard definition of BOO	Mean age, yr	Mean IPSS (range)	Prevalence of BOO (%)	Sensitivity	Specificity	PPV	NPV
Abdel-Aal et al. 2011	DWT	2mm	BOOI >40	58.7 (50-72)	12.45 (6.5 - 25)	30	65.7	76	65.7	76
ElSaied et al. 2013	DWT	2mm	BOOI >40	61.7 (53-76)	13.4 (4 - 22)	46	82.7	92.6	90.5	86.2
Franco et al. 2010	DWT	6mm	BOOI >40	67 (48-80)	15 (9 - 25)	76	73	82	90	50
Kessler et al. 2006	DWT	1.5mm	BOOI >40	67 (59-77) (Median)	17 (no BOO), 22 (BOO) (median)	60	100	15	64	100
		2mm					92	68	81	85
		2.5mm					69	88	89	65
		2.9mm					43	100	100	54
Oelke et al. 2002	DWT	2mm	CHESS	63 (42-82)	14.4 (2 - 29)	47	63.6	97.3	95.5	75
Oelke et al. 2007	DWT	2mm	BOOI >40	62 (40-89) (Median)	15 (2 - 30) (Median)	47	83	95	94	86
Aganovic et al. (a) 2012	BWT	5mm	BOOI >40	65.4 (48-82)	18.2 (6 - 31)	49	64.5	59.2	NR	NR
Manieri et al. 1998	BWT	5mm	URA>29	64.5 (34-88)	14.91 (0-29)	57	55.4	91	87.9	63.4

Bladder weight

Study	Index test	Threshold value	Reference standard definition of BOO	Mean age, yr	Mean IPSS (range)	Prevalence of BOO (%)	Sensitivity	Specificity	PPV	NPV
Han et al. 2011	Corrected UEBW (UEBW/BSA)	27.86gm	BOOI >40	63.5	19.9	26	61.9	59.8	33.8	82.6
Kojima et al. 1997	UEBW	35gm	BOOI >40	71 (45-89)	NR	52	85.3	87.1	87.9	84.4

External condom method

Study	Threshold value	Reference standard definition of BOO	Mean age, yr	Mean IPSS (range)	Prevalence of BOO (%)	Sensitivity	Specificity	PPV	NPV	Comments
Pel et al. 2002	Qmax/Pext Max	BOOI >40	62 (no BOO), 51 (equivocal), 62 (BOO)	NR	29	90.9	92.3	96.7	80	This is in the 46 out of 75 patients (61.3%) who were able to successfully perform the non-invasive test

Intravesical prostatic protrusion

Study	Threshold value	Reference standard definition of BOO	Mean age, yr	Mean IPSS (range)	Prevalence of BOO (%)	Sensitivity	Specificity	PPV	NPV
Aganovic et al. (a) 2012	10mm	BOOI >40	65.4 (48-82)	18.2 (6 - 31)	49	59.6	81.4	73.8	69.6
Chia et al. 2003	10mm	BOOI >40	64.6 (50-94)	20.3	63	76	92	94	69
Dicuio et al. 2005	10mm	DAMPF score	67.9 (47-86)	22.4 (6 - 35)	64	NR	NR	100	NR
Lim et al. 2006	10mm	BOOI >40	66 (52-88) (Median)	12 (1-32) (Median)	49	46	65	72	46
Reis et al. 2008	10mm	BOOI >40	64 (56-73)	13 (6 - 20)	48	80	68.2	69.6	78.9
Abdel-Aal et al. 2011	8mm	BOOI >40	58.65 (50-72)	12.45 (6.5 - 25)	30	80	80	73.7	85.1
Aganovic et al. (b) 2012	12mm	BOOI >40	65.3 (48-80)	18.2 (6 - 31)	NR	59.6	81.3	73.8	69.6
Franco et al. 2010	12mm	BOOI >40	67 (48-80)	15 (9 - 25)	76	65	77	88	47
Keqin et al. 2007	8.5mm	BOOI >40	71 (55-84)	16.8 (grade 1-2 IPP) v 18.6 (grade 3 IPP)	NR	75	82.6	NR	NR
Pascual et al. 2011	10.5mm	BOOI >40	61.6 (BOO), 64.7 (No BOO)	14.7 (BOO) 13.7 (no BOO)	54	90.5	72.2	76	85
Reis et al. 2008	5mm	BOOI >40	64 (56-73)	13 (6 - 20)	48	95	50	63.3	91.7

Doppler ultrasound

Study	Threshold value	Reference standard definition of BOO	Mean age, yr	Mean IPSS (range)	Prevalence of BOO (%)	Sensitivity	Specificity	PPV	NPV
Belenky et al. 2003	RI T>0.05	BOOI >40	65.6 (46-76)	NR	75	NR	NR	95	57
Ozawa et al. 2000	VR >1.6	BOOI >40	NR	NR	60	NR	NR	100	NR

Prostate volume or height

Study	Index test	Threshold value	Reference standard definition of BOO	Mean age, yr	Mean IPSS (range)	Prevalence of BOO (%)	Sensitivity	Specificity	PPV	NPV
ElSaied et al. 2013	Prostate volume	25ml	BOOI >40	61.7 (53-76)	13.4 (4 - 22)	46	87	29.6	51.3	72.7
Franco et al. 2010	Prostate height	40mm	BOOI >40	67 (48-80)	16 (9 - 25)	76	68	54	82	48
	Prostate volume	38ml					72	61	84	44
Lim et al. 2006	Prostate volume	40ml	BOOI >40	66 (52-88) (Median)	12 (1-32) (Median)	49	51	38	65	42
Watanabe et al. 2002	Prostate volume and H:W	30ml and 0.8	LinPURR ≥3	66.4 (49-84)	NR	47	42	100	NR	NR

Near infrared spectroscopy

Study	Threshold value	Reference standard definition of BOO	Mean age, yr	Mean IPSS (range)	Prevalence of BOO (%)	Sensitivity	Specificity	PPV	NPV
Macnab et al. 2008	NIRS algorithm	Not defined	67.3 (50-91) (BOO), 56.8 (40-77) (no BOO)	20.2 (no BOO), 19.6 (BOO)	49	85.71	88.89	88.89	85.71
Yurt et al. 2012	NIRS algorithm	BOOI >40	58.8	17.8	55	86	87.5	89.2	84
Zhang et al. 2013	NIRS algorithm	BOOI >40	68.5 (56-85)	NR	72	68.3	62.5	82.7	42.9
Chung et al. 2010	Downward pattern on free flow	BOOI >40	67	19	79	34.6	42.9	69.2	15
Chung et al. 2010	Downward pattern on pressure-flow study	BOOI >40	NR	NR	79	61.1	40	78.6	22.2
Stothers et al. 2010	CART model	BOOI >40	62 (49-91)	19 (12-34)	47	100	87.5	93.8	100

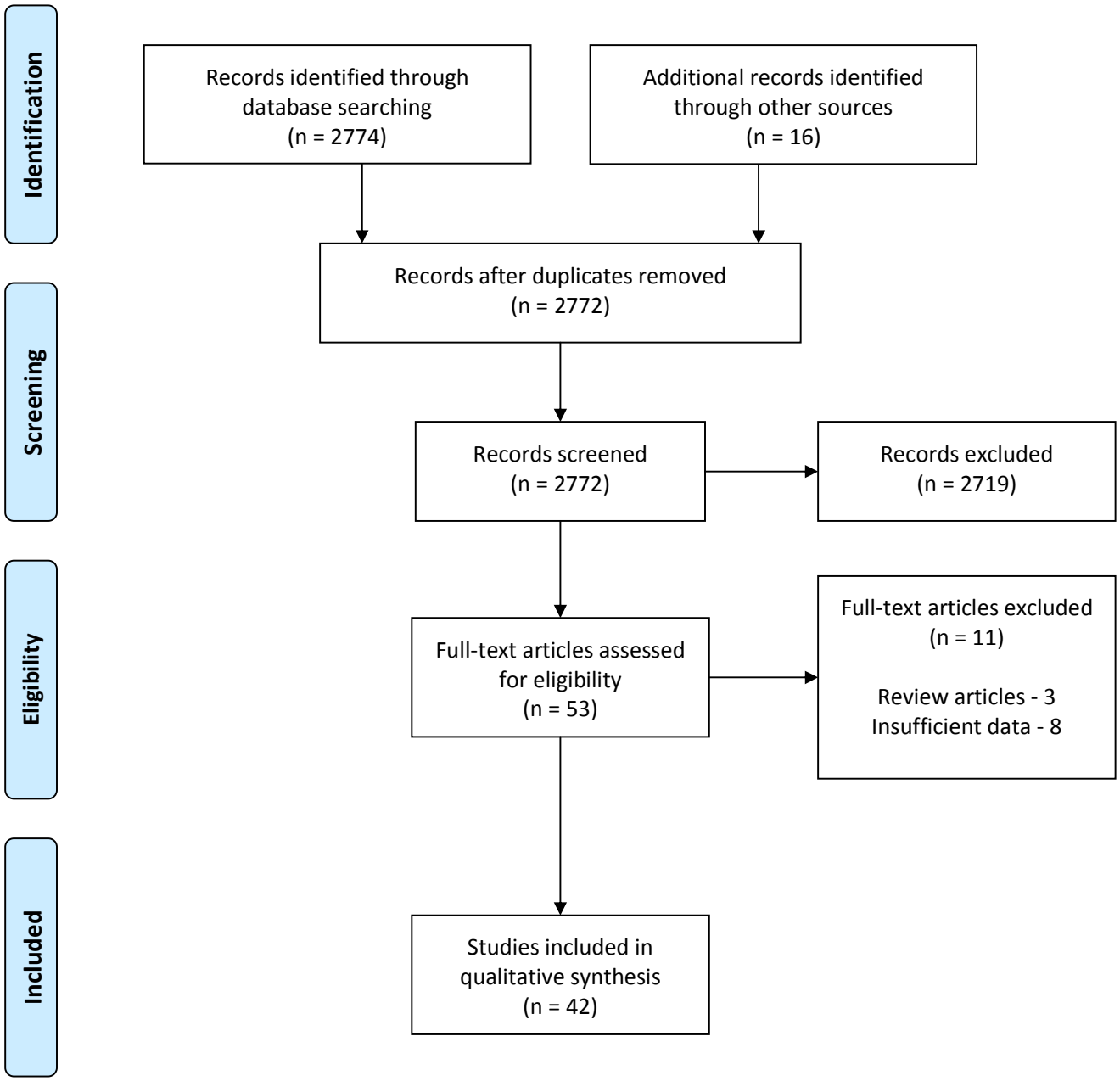
Table 3 (a). Summary of results for each type of index test (grouped)

Test	No. of studies	No. of patients	Median sensitivity (IQR)	Sensitivity range	Median specificity (IQR)	Specificity range	Median PPV	PPV range	Median NPV	NPV range
Penile Cuff test	7	546	88.89 (76.5-95.3)	64 - 100	70.2 (64.5-78.3)	55.6 - 84	69 (67.9 - 72.5)	66.7 - 92	93 (89.2-100)	78 - 100
Uroflowmetry	16	2580	72 (58.4 - 89.9)	16 - 100	64 (38.5 -81)	25 - 100	70 (57.5 - 79)	32.5 - 100	70 (57.7 - 85.2)	46.5 - 100
Detrusor wall thickness	8	848	69 (64-82.8)	43 - 100	88 (72-93.8)	15 - 100	89.5 (82.7-93.1)	64 - 100	75.5 (63.8-85.7)	50 - 100
Bladder weight	2	258	73.6	61.9 - 85.3	73.45	59.8 - 87.1	60.85	33.8 - 87.9	83.5	82.6 - 84.4
External condom catheter	1	56	90.9		92.3		96.7		80	
Intravesical prostatic protrusion	10	1013	75.5 (60.9-80)	46 - 95	78.5 (69.2-81.3)	50 - 92	73.8 (72.4-85)	69.6 - 100	69.6 (69 - 85)	46 - 85.1
Doppler ultrasound	2	51	No data	No data	No data	No data	97.5 (96.2-98.7)	95 - 100	57	No data
Prostate volume	3	245	72 (61.5-79.5)	51 - 87	38 (33.8-49.5)	29.6 - 61	65 (58.1-74.5)	51.3 - 84	44 (43-58.3)	42 - 72.7
NIRS	5	282	85.71 (68.3-86)	61.1 - 100	87.5 (62.5-87.5)	40 - 87.5	88.89 (82.7-89.2)	78.6 - 93.8	84 (42.9-85.71)	22.2 - 100

Table 3 (b). Summary of results for each type of index test using the most commonly used threshold values relevant to each test (grouped)

Test	Threshold value	No. of studies	No. of patients	Median sensitivity (IQR)	Range	Median specificity (IQR)	Range	Median PPV (IQR)	Range	Median NPV (IQR)	Range
Penile Cuff test	Griffiths nomogram	3	243	88.9 (76.4-94.4)	64 - 100	75.7 (69.3 - 78.3)	63 - 81	67.7 (67.2 - 67.9)	66.7 - 68	93 (85.5 - 96.5)	78 - 100
Uroflowmetry	10ml/s	13	2257	68.3 (55.1 - 74.2)	29 - 100	70.5 (62.3 -89.7)	37 - 100	74.3 (66-89.5)	38.4 - 100	68 (54-76)	46.5 - 100
Detrusor wall thickness	2mm	5	467	82.7 (65.7-83)	63.6 - 92	92.6 (76-95)	68 - 97.3	90.5 (81-94)	65.7 - 95.5	85 (76-86)	75 - 86.2
Intravesical prostatic protrusion	10mm	5	473	67.8 (56.2-77)	46 - 80	74.8 (67.4-84)	65 - 92	73.8 (72-94)	69.6 - 94	69.3 (63.2-71.9)	46 - 78.9
NIRS	NIRS algorithm	3	195	85.71 (77-85.8)	68.3 - 86	87.5 (75-88.1)	62.5 - 88.9	88.89 (85.7-89)	82.7 - 89.2	84 (63.4-84.8)	42.9 - 85.71

Illustration



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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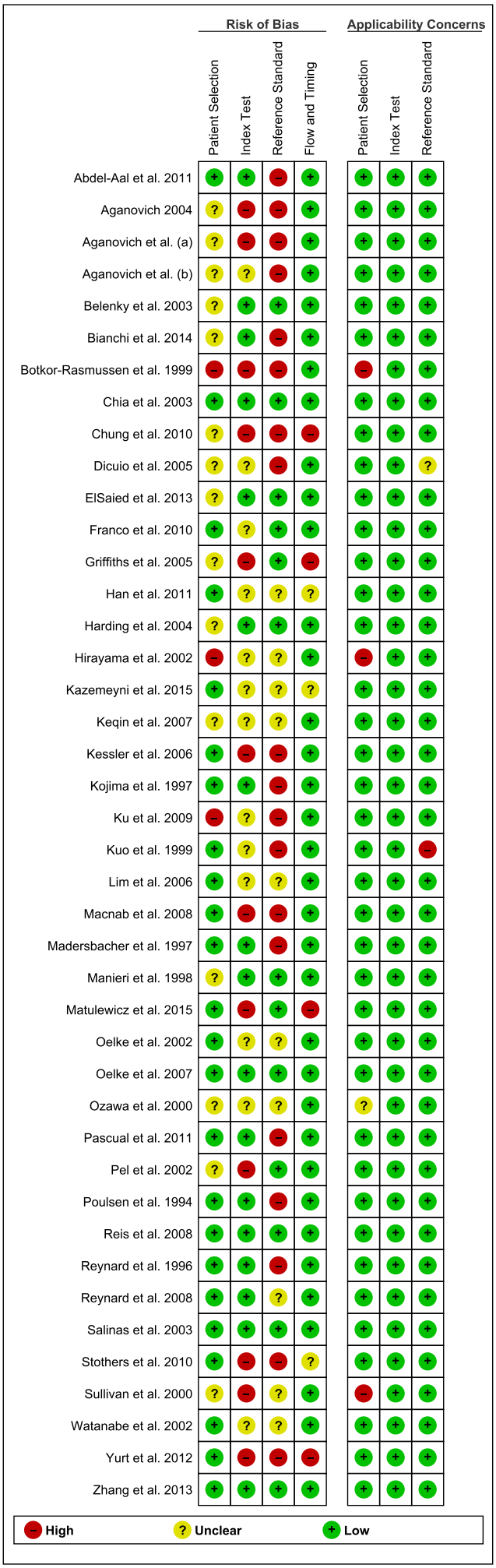
Risk of Bias
Applicability Concerns
Patient Selection
Index Test
Reference Standard
Flow and Timing
Patient Selection
Index Test
Reference Standard
Abdel-Aal et al. 2011
Aganovich 2004
Aganovich et al. (a)
Aganovich et al. (b)
Belenky et al. 2003
Bianchi et al. 2014
Botkor-Rasmussen et al. 1999
Chia et al. 2003
Chung et al. 2010
Dicuio et al. 2005
ElSaied et al. 2013
Franco et al. 2010
Griffiths et al. 2005
Han et al. 2011
Harding et al. 2004
Hirayama et al. 2002
Kazemeyni et al. 2015
Keqin et al. 2007
Kessler et al. 2006
Kojima et al. 1997
Ku et al. 2009
Kuo et al. 1999
Lim et al. 2006
Macnab et al. 2008
Madersbacher et al. 1997
Manieri et al. 1998
Matulewicz et al. 2015
Oelke et al. 2002
Oelke et al. 2007
Ozawa et al. 2000
Pascual et al. 2011
Pel et al. 2002
Poulsen et al. 1994
Reis et al. 2008
Reynard et al. 1996
Reynard et al. 2008
Salinas et al. 2003
Stothers et al. 2010
Sullivan et al. 2000
Watanabe et al. 2002
Yurt et al. 2012
Zhang et al. 2013
High
Unclear
Low

Take home message

A number of non-invasive tests have been studied for the diagnosis of BOO in men with LUTS and found to have a high sensitivity and specificity but high heterogeneity. Despite these promising results of the non-invasive assessment of BOO, pressure-flow study remains the gold standard test.

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