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Sam E. Mason, Alasdair J. Scott, Erik Mayer, Sanjay Purkayastha

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Patient-Related Risk Factors for Urinary Retention Following Ambulatory

General Surgery; a Systematic Review and Meta-Analysis

Sam E Mason[a], Alasdair J Scott[a], Erik Mayer[a], Sanjay Purkayastha[a]

[a]Academic Surgical Unit, Imperial College London, UK

Corresponding Author:

Dr Sam Mason BSc (Hons), MBBS, MRCS

Address: Division of Surgery, Imperial College London, 10th Floor Queen Elizabeth the Queen Mother Building, St Mary's Hospital Campus, South Wharf Road, London, W2 1NY.

Email: sam.mason06@imperial.ac.uk

Telephone: +442033126666

Co-Authors:

Dr Alasdair Scott BSc (Hons), MBBS, PhD. Email: alasdair.scott03@imperial.ac.uk

Dr Erik Mayer BSc (Hons), MBBS, PhD, FRCS. Email: e.mayer@imperial.ac.uk

Dr Sanjay Purkayastha BSc, MBBS, MD, FRCS. Email: s.purkayastha@imperial.ac.uk

Abstract

Background

Post-Operative Urinary Retention (POUR) is a source of avoidable patient harm. The aim of this review is to identify and quantify the role of patient-related risk factors in the development of POUR following ambulatory general surgery.

Methods

Studies published until December 2014 were identified by searching MEDLINE, EMBASE and PsycINFO databases. Risk factors assessed in three or more studies were meta-analysed.

Results

Twenty-one studies were suitable for inclusion consisting of 7802 patients. The incidence of POUR was 14%. Increased age and the presence of lower urinary tract symptoms significantly increased risk with ORs of 2.11 (95% CI 1.15-3.86) and 2.83 (1.57-5.08) respectively. Male sex was not associated with developing POUR - OR 0.96 (0.62-1.50). Pre-operative α-blocker use significantly decreased the incidence of POUR with an OR 0.37 (0.15-0.91).

Conclusions

Increased age and the presence of lower urinary tract symptoms increases the risk of POUR, whilst α-blocker use confers protection. Male sex was not associated with POUR. These findings assist in pre-operative identification of patients at high risk of POUR.

Keywords: Systematic Review, Urinary Retention, Surgical Treatment, Risk Factors

Background

Post-Operative Urinary Retention (POUR) refers to the inability to initiate adequate micturition despite bladder distension in the early post-operative period[1]. It has been described as a complication of day-case general surgery for over 50 years but remains a common problem in modern day surgical practice, with reported incidences up to 49%[2].

POUR is an obstacle in the provision of high quality surgical care. It results in an increased morbidity for patients including the risks associated with bladder catheterisation (urinary tract infection) and the psychological consequences of an unexpected surgical complication. POUR is responsible for 20-25% of unexpected inpatient admissions following day-case general surgery[3,4], which has a direct cost implication to the institution but may also threaten the ability to accept elective operative admissions. Even when POUR is managed on an out-patient basis, the institution will need to provide a pathway to manage this, typically requiring urologist and specialist nurse clinics. The transition away from in-patient surgery with routine bladder catheterisation and towards day-case procedures means the impact of POUR on surgical care is only going to increase. Furthermore, ever-increasing financial pressures have stimulated a drive towards increased efficiency in the provision of healthcare services. This is threatened by conditions such as POUR, where unexpected and potentially unnecessary costs may divert limited resources from providing high quality care.

Optimisation of the day-case surgical pathway can be achieved with pre-operative identification of patients at high risk of POUR and initiation of prophylactic interventions. In order to achieve risk prediction on a patient level it is necessary to understand the role and interplay of the factors which increase the risk of, or provide protection against, POUR. Within ambulatory general surgery, several risk factors have been established relating to operative factors (including equipment and technique[5-12]) and anaesthetic factors (including intravenous fluid use and route of anaesthesia[13-23]). However there is a paucity of work on the influence of *patient-related* factors. Patient-related factors are those unrelated to the surgery or anaesthesia and are pre-operatively identifiable, likely to include demographic data, comorbid status and pharmacological history.

The aim of this systematic review with meta-analysis is to appraise the literature to identify and quantify the influence of patient-related risk factors on the development of POUR after day-case general surgery.

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Methods

A systematic review with meta-analysis was carried out in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[24].

Literature Search Strategy

General surgical procedures that could be performed in an ambulatory setting were identified after discussion and consensus between the authors. A search strategy was then designed to identify studies published in peer reviewed journals which report the risk factors for developing POUR after such procedures, using terms including '(urine OR urinary) AND retention', '(void* OR micturi*) AND (dysfunction OR difficult*)', 'post-operative', 'general surg*' and 'anorectal'. Using Ovid SP©, the following electronic databases were searched until the fourth week of December 2014 for English language articles: MEDLINE (1950-present), Embase (1947-present) and PsycINFO (1806-present). In addition the bibliographies of review articles returned in the search were examined to identify any additional studies of interest.

Criteria for Study Inclusion

Two authors (S.M. and A.S.) independently applied the inclusion criteria to the search results. This was achieved by initial title and abstract screening followed by retrieval of manuscripts for all studies that could not be excluded at the screening stage or where an abstract was not available. For inclusion, studies must use an experimental or observational design to compare the incidence of POUR across at least two cohorts defined by the presence or absence of a specified patient-related risk factor. Patient-related risk factors are defined as pre-operatively identifiable and unrelated to the surgery or anaesthesia, such as demographic data, comorbid status and pharmacological history. All patients must have been age sixteen or over at the time of surgery. Studies were excluded if they did not present primary data (review articles, commentaries) or were abstracts published in conference proceedings.

Surgical Intervention

For inclusion in this review, the surgical intervention must be usually performed by a general surgeon and be possible to be performed on a day-case basis. The following procedures were deemed suitable: abdominal wall hernia repair (open or laparoscopic), anorectal procedures for anal fissures, fistulas, haemorrhoids and abscesses; laparoscopic cholecystectomy, pilonidal sinus excision, mucosal resection for rectal prolapse, Nissen's fundoplication and Heller's myotomy. In the case of two or more simultaneous surgical procedures, it was necessary that all fulfil the criteria of a suitable surgical intervention as stated here. Surgical procedures for the purpose of weight reduction or for malignant conditions were excluded. As routine intra-operative bladder catheterisation was used variably between institutions, and given its nature as a potential confounder and intervention to decrease the incidence of POUR, studies were excluded if there was a statistically significant difference in the rate of intra-operative catheterisation between the cohorts of interest.

Definition of Post-Operative Urinary Retention

POUR was defined as post-operative patient catheterisation for difficulty in voiding or if the authors used the term 'urinary retention'. In order for the urinary retention to be considered 'post-operative', it needed to be in the early post-operative period, typically less than 24 hours.

Data Extraction

One author (S.M.) extracted the following data from each included study into a Microsoft Excel© 2010 (Microsoft Corporation, Redmond, Washington, USA) database: author, year, study design, number of patients, surgical procedure undertaken, risk factor examined and the incidence of POUR in each cohort. Study design was described as prospective or retrospective, with the former defined as identification of the potential risk factor pre-operatively with future detection of POUR. Retrospective studies in this setting were case-control by design, post-operatively identifying patients in POUR and then collecting data on potential pre-operative risk factors. Within the prospective group, studies were described as randomised controlled trials (RCT) only if the patient-related risk factor of interest was allocated by randomisation.

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Statistical Analysis

All analyses were performed in R (Foundation for Statistic Computing, Vienna, Austria) using the metafor package[25]. It was required that studies presented discrete data. The incidences of POUR in the risk factor and control cohorts were used to calculate odds ratios. Where three or more independent studies had evaluated a risk factor, the odds ratios were pooled using a random-effects model (restricted maximum likelihood approach) to generate a summary odds ratio and 95% confidence interval. A random effects model was used after significant functional differences were found on examination of study manuscripts. P values were calculated for comparison against the null hypothesis of no effect (OR = 1). The I^2 statistic and Cochran's Q test were used to quantify heterogeneity between studies. To assess the influence of individual studies on the summary effect size, a sensitivity analysis was performed whereby the model was repeatedly fitted with sequential omission of each study. Where appropriate, funnel plots were generated and tested for asymmetry by regression to diagnose publication bias[26]. A P value less than or equal to 0.05 was considered significant.

The quality of the included studies was assessed using a Jadad score[27] or the Newcastle-Ottawa scale (NOS)[28], which have been validated for randomised and non-randomised studies respectively. The Jadad score assesses randomisation, blinding and completeness of follow-up with a maximum score of five, where below three represents low methodological quality. The NOS can be applied to prospective or case-control studies where a maximum of nine stars can be awarded based on criteria such as follow-up, cohort comparability and selection of controls; a score of below six considered low quality.

Where appropriate, subgroup analyses were performed based on study design and methodological quality.

Results

The search identified 3759 potential studies, 3714 from electronic bibliographies and 45 from review articles by hand searching. The majority were excluded at abstract screening, most commonly for inappropriate procedure or study design, with 570 manuscripts reviewed in full (Figure 1).

Twenty-one studies were deemed suitable for inclusion (Table 1). In total 7802 patients were included with an overall POUR incidence of 14%. All procedures involved either groin hernia repairs or anorectal procedures including abscess drainage, lateral sphincterotomy and haemorrhoidectomy. All analyses were undertaken on study groups receiving exclusively hernia repairs or anorectal procedures, with no mixture of cases.

Ten patient-related factors were identified in the included studies: age, gender, pre-operative α-adrenoceptor blocker use, previous lower urinary tract symptoms (LUTS), benign prostatic hyperplasia (BPH), prostate cancer, American Society of Anesthesiologists (ASA) score, previous urinary retention, human immunodeficiency virus (HIV) infection and diabetes mellitus. Of these, age, gender, LUTS and pre-operative α-blocker use were investigated in three or more manuscripts and were therefore suitable for meta-analysis.

Methodological Quality

Of the twenty-one included studies, four were RCTs, seven were prospective cohort and the remaining ten were case-control. Jadad and NOS assessment showed median scores of 2 (range 1-4) and 6 (range 5-8) respectively, with five studies considered of low methodological quality. The only patient-related risk factor in the meta-analysis to be assessed using only prospective studies was the role of α-blockers, where the criteria for patient selection, method of allocation and blinding were either inadequate or not described in the majority of studies. Three of the five studies[29,32,33] assessing α-blockers were considered of poor methodological quality with high risk of systematic bias.

The role of gender, age and LUTS were all evaluated by pooling prospective and retrospective studies at a ratio of approximately 1:2. LUTS, the only subjective factor in the meta-analysis, was defined by only one study[40] and retrospectively applied in four of the six. Despite none of these studies being considered of low methodological quality on NOS assessment, the authors considered these papers at high risk of selection and reporting biases.

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When assessing the role of age, authors arbitrarily defined an age threshold to divide their patients into high and low age groups, with 50, 55 and 70 years most commonly used. In two of the four retrospective studies, it appears that the age cut-off was defined *post-hoc*, likely after initial analysis of the data. One study was considered of low methodological quality, retrospective by design and unable to account for a lack of baseline similarity between the cohorts.

No studies on the role of gender were considered of low methodological quality on NOS assessment. Although gender was rarely a pre-defined factor of interest in the risk of developing POUR, this was considered to have a low risk of bias on the results.

Description of Results

Gender

Ten studies[36-40,42,45-48] (5624 patients) assessed the influence of gender on the risk of developing POUR. The only two studies that demonstrated a significant relationship both identified male gender as protective[40,45], however once the studies had been pooled, male sex was not found to significantly influence the risk of developing POUR with a summary OR of 0.96 (figure 2, 95% CI 0.62-1.50, p=0.87). Including only prospective studies did not affect the lack of association between sex and POUR (data not shown).

Age

Eight studies[34-41] (5407 patients), one of which presented two distinct cohorts (based on the surgical procedure)[36], assessed the influence of age. Overall, older patients had a significantly increased risk of POUR compared to younger patients with a summary OR of 2.11 (figure 3, 95% CI 1.15-3.86, p=0.02). Sub-group analyses were conducted with studies using age cut-offs of ≥50, ≥55 and ≥60 years (Figure 4). This demonstrates a marked increase in risk once age cut-offs of ≥60 years were used, with a summary OR of 7.09 (95% CI 2.79-18.03). Exclusion of low quality or retrospective studies continued to demonstrate a significant association between increased age and POUR (data not shown).

Lower Urinary Tract Symptoms

When referring to symptoms of the lower urinary tract, authors either used the term 'LUTS' or 'BPH', with all but one giving no definition of these terms. For the purpose of the analysis it was considered that these two groups were indistinct and they were pooled under the term 'LUTS'. The six studies[8,36,37,40-42] (3821 patients) demonstrated that a history of LUTS significantly increased the risk of POUR with a summary OR of 2.83 (figure 5, 95% CI 1.57-5.08, p=<0.001).

Pre-Operative α-Blocker Use

Five studies[29-33] (455 patients) assessed the influence of pre-operative α-blocker use on the incidence of POUR, three with prazosin and one each with phenoxybenzamine and tamsulosin. Four were RCTs and all were within the context of an interventional trial. The time of the first α-blocker dose being administered varied between 6 and 24 hours pre-operatively across the studies. Three studies[29,30,32] were conducted exclusively in male patients while the gender of the patients in the remaining two[31,33] was unclear. Overall, α-blocker use was found to significantly reduce the risk of POUR with a summary OR of 0.37 (figure 6, 95% CI 0.15-0.91, p=0.03). If any of the studies of low methodological quality are removed from the analysis, the significant protection from α-blockers is no longer demonstrated. Eggers regression test for funnel plot asymmetry was negative (p=0.85).

Additional Patient-Related Risk Factors

Five studies[8,40,42-4] described the further patient related-risk factors for which there was insufficient data for meta-analysis. ASA grades 3-4 (compared to 1-2) was a significant risk factor for POUR shown in one study with an OR of 6.75 (1.30-35.17). Previous urinary retention or HIV infection were not shown to significantly increase the risk of POUR. Diabetes mellitus and the presence of prostate cancer were each assessed by two

studies and in both cases one study found a significantly increased risk with the other demonstrating

equivalence.

Heterogeneity and Sensitivity Analysis

As expected from the inherent variability in study methodology, there was significant inter-study

heterogeneity evidenced by Cochrane's Q tests and I^2 values for the analyses of age, sex and LUTS. Tests for

heterogeneity were not significant for α-blocker analysis (Q=6.45, p=0.17, I^2=23%). However, visual

inspection of the relevant forest plot (Figure 2) and the size of the standard error for the pooled estimate

(0.468) indicated a large degree of variation *within* each study. In combination with the low number of

studies available, this is likely to render any tests of heterogeneity underpowered. These heterogeneity data

support the application of a random effects model in carrying out the meta-analyses. Refitting the models

with sequential removal of each study had no significant impact on the summary effect sizes for age, gender

or LUTS (data not shown). The α-blocker analysis was not so robust as removal of any one of four

studies[29,31-33] resulted in the 95% confidence intervals for the new summary effect sizes overlaping 1,

indicating no effect (data not shown).

Discussion

This meta-analysis aimed to identify patient-related risk factors for the development of POUR following

ambulatory general surgery and demonstrated that increased age and pre-operative LUTS significantly

increased the risk of POUR, whilst pre-operative α-blocking medications provided significant protection.

Of the five studies which evaluated interventional prophylactic use of α-blockers, four demonstrated no

significant difference in the incidence of POUR; however the pooled estimate indicated that these agents are

protective in this setting. There was no significant heterogeneity identified between these studies based on

the Cochran Q score, however all demonstrated poor accuracy with large 95% CIs; reflected in the CI of the

pooled estimate ranging from 0.15 to 0.91. It was determined upon manuscript examination that these studies

are in fact heterogeneous when considering factors including surgical procedure and anaesthetic type. Given the small number of studies and the large intra-study variance, the statistical tests of heterogeneity are almost certainly underpowered. The intra-study variance also means that although the data suggests α-blockade is protective, no clinically meaningful estimate as to the extent of that protection can be given. It is also important to consider the timing that the α-blockers were administered pre-operatively, with all studies giving them less than 24 hours pre-operatively. Although the product literature of a common α-blocker (tamsulosin) describes a peak plasma concentration at 4-7 hours, it is possible that more than 24 hours is required for these agents to exert a maximum clinical effect. As a result, many of the studies included in this review may show a false lack of association and there is a need for an adequately powered randomised controlled trial with a greater period of pre-operative α-blocker administration. Additionally, given that the majority of studies were conducted with a male population, the role of these agents in a female population needs to be assessed. This will determine with greater precision the benefit surgeons and patients can expect from prophylactic α-blocker use.

Eight studies in this review demonstrated increased age as a risk factor for POUR, a finding which has been shown following many types of surgery in the ambulatory and inpatient settings[1,49-53]. Sub-group analysis demonstrated a marked increase in the risk of POUR once an age cut-off of ≥60 years was used. The discrete nature of the data only allowed three sub-group analyses, but this data suggests that patients over the age of 60 should be considered at increased risk.

Male gender, although understood to be a risk factor for non-operative urinary retention, has been shown across the nine studies here not to be a risk factor for POUR. This is consistent with the literature across other surgical specialities including orthopaedics, thoracic, vascular and otolaryngology; where neither gender has been consistently identified to confer risk[49-51,54].

Pre-operative LUTS have been demonstrated in this analysis to increase the risk of POUR in what was a largely mixed gender population. This finding is consistent with patients undergoing orthopaedic surgery, where LUTS increases the risk of POUR independent of gender[55]. It is apparent that there are no established definitions being applied for the terms LUTS and BPH, which appear to be used interchangeably to describe subjective symptoms including frequency, urgency, straining and weak stream. The fact that only one study

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defined LUTS or BPH limits the external validity of the finding that this cohort of patients are at risk factor of POUR. It is recommended that future studies state the definition of terms such a 'lower urinary tract symptoms'.

The quality of the data in the literature and that several potentially confounding factors are at play means it is not possible to draw conclusions either about the mechanism by which the micturition pathway is disrupted in POUR or the interaction between patient-related risk factors.

The methodological quality of the studies in this area provide the greatest challenge in understanding POUR and also provides a potential source of bias in this analysis. Given the nature of patient-related risk factors and in particular that they are often non-modifiable, it is rarely possible to perform randomised controlled trials. However ten of the twenty-one studies were retrospective case-control design. Case-controlled studies are more likely than their prospective counterparts of making errors due to recall, observer and reporting biases. Furthermore they are less capable in identifying confounding factors for which sufficient data can be collected to identify risk factors in multi-variant analysis. Subgroup analyses were performed based on study design and methodological quality, which determined there was no evidence of such biases influencing the results. This may have been due to the inability of the NOS to adequately distinguish between high and low quality surgical trials. It was found that all studies were awarded quality stars for 'ascertainment of exposure' (the surgical procedure) and adequacy of follow-up (the immediate post-operative period). However this acted to dilute the influence of likely a more differentiating factor (comparability of cohorts), for which only one star is available. This highlights the need for quality scoring systems more suited to surgical trials.

A further challenge in pooling data for this meta-analysis was that studies often used varying cut-offs or definitions for factors of interest, sometimes giving no definition at all. This was encountered when considering an age cut-off to define a high risk patient, a time to administer prophylactic α-blockers or a definition of the term LUTS.

It is apparent from this review how poorly the group of patients at risk of POUR is understood. In the consideration of patient risk management and cost-efficient service delivery, this review has several implications for practice both in the community and within the surgical setting. POUR is common and a significant cause of admission to hospital following ambulatory general surgery. When overnight admission

occurs the 11-70% cost saving expected from an ambulatory pathway will be obviated[56]. When patients are managed as an outpatient with an indwelling urinary catheter they are at a 5% per day risk of a urinary tract infection with 2-4% of those developing bacteraemia[57,58]. The impact of this on both patients and healthcare institutions is apparent when considering that 34.7 million ambulatory surgery visits were made in the USA in 2006 alone, an ever increasing figure[59]. It is likely that both increased age and symptomatic voiding dysfunction are risk factors for POUR. Therefore in order to provide high quality care it is necessary to identify these patients at the earliest stage, often in the primary sector upon referral for surgical assessment. POUR is potentially predictable and preventable. This provides an opportunity to intervene pre-operatively and manage the patient expectedly. Effective prophylactic interventions already exist and include avoiding high risk surgical and anaesthetic techniques (such as spinal anaesthesia), or measures as simple as limiting post-operative oral fluid intake. The latter has been shown in an RCT to reduce the incidence of POUR from 15 to 4%[23]. Optimising the ambulatory surgery pathway to identify high risk patients as early as possible to initiate interventions will be the most effective way of decreasing the financial and morbidity burden of POUR. Furthermore identifying high risk patients pre-operatively will maximize the cost/benefit/risk profile of any interventions made. This most likely requires development of a validated risk score, which incorporates patient, surgical and anaesthetic-related factors to define risk on an individual level.

Conclusion

This study has demonstrated that increased age and the presence of pre-operative LUTS are risk factors for developing post-operative urinary retention following ambulatory general surgery. Prophylactic use of α-adrenoceptor antagonists appears to decrease the incidence of POUR however there is a need for an adequately powered randomised controlled trial in this setting. The ambulatory surgery pathway needs to be optimised to pre-operatively identify high-risk patients at whom prophylactic interventions can be targeted.

Disclosure

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Figure Captions

Figure 1 – PRISMA flowchart denoting the process to include eligible studies.

Abbreviation: RCT- randomized controlled trial.

Figure 2 - Forest plot depicting the effect of gender.

Figure 3 - Forest plot depicting the effect of age.

Figure 4 - Forest plot of age sub-group analysis.

Figure 5 - Forest plot depicting the effect of lower urinary tract symptoms.

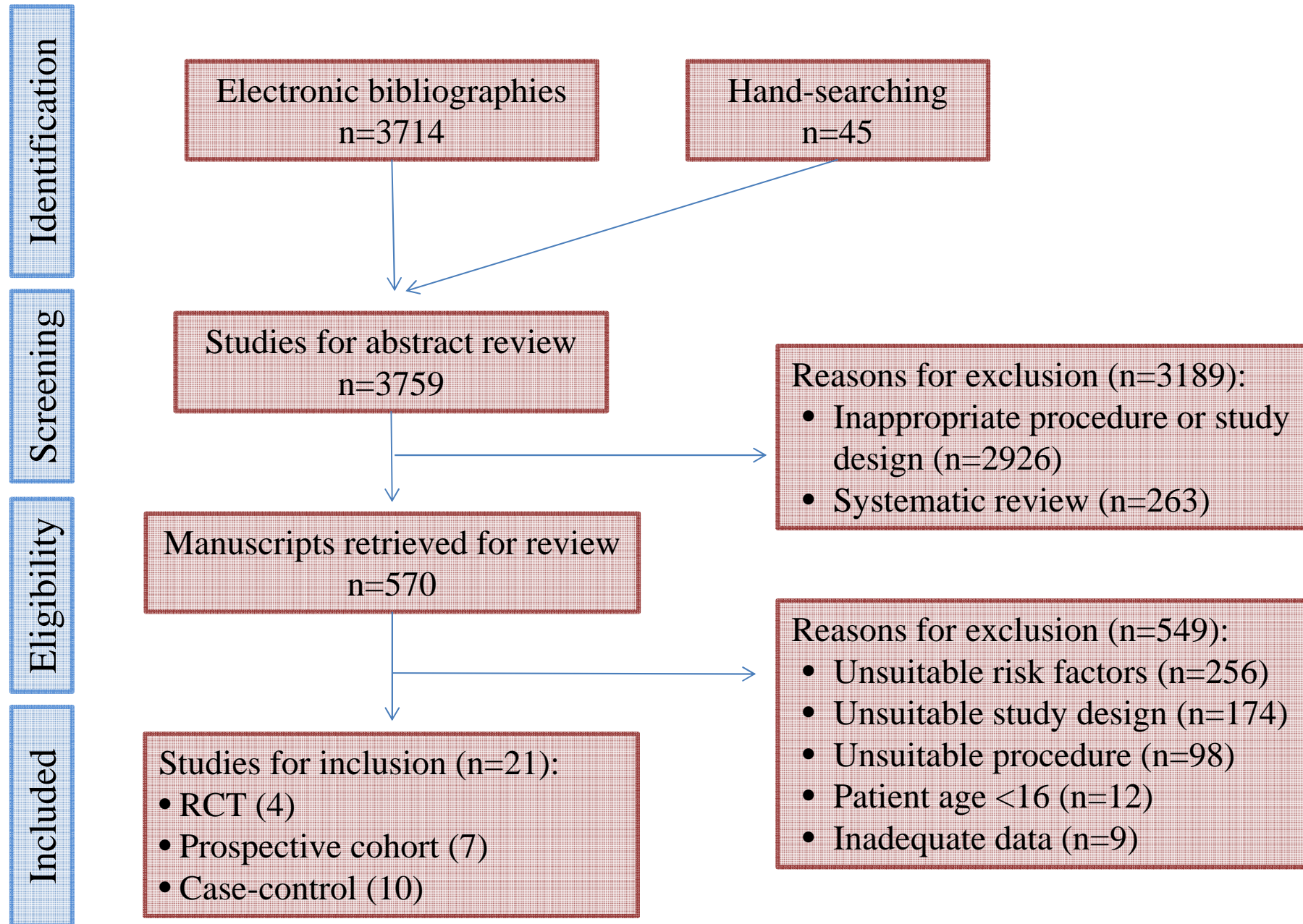Figure 6 - Forest plot depicting the effect of α-blocker usage.

Table 1

Author	Year	Study Design	Operation	*n*	Risk Factor	Quality Score[a]	Odds Ratio (95% CI)
Mohammadi-Fallah[29]	2012	RCT	IH	80	α-blocker	2	0.15 (0.02-1.27)
Woo[30]	1995	Prospective	IH	70	α-blocker	7	5.00 (0.23-108)
Cataldo[31]	1991	RCT	Anorectal	49	α-blocker	4	0.67 (0.22-2.07)
Gonullu[32]	1999	RCT	IH	156	α-blocker	2	0.23 (0.06-0.87)
Goldman[33]	1988	RCT	IH	102	α-blocker	1	0.06 (0.00-0.14)
Beltran[34]	2006	Prospective	IH	688	Age >70	7	12.43 (5.96-26.0)
Amato[35]	2012	Case-Control	IH	218	Age >70	5	3.34 (0.37-30.4)
Zaheer[36]	1998	Case-Control	Hemorr.	382	Age >55	6	1.25 (0.82-1.91)
			Anorectal	645	Age >47		2.30 (1.07-4.93)
			Hemorr, Anorectal	1027	LUTS		1.85 (1.04-3.30)
			Hemorr, Anorectal	1027	Male		1.23 (0.87-1.75)
Eftaiha[37]	1980	Prospective	Anorectal	263	Age >55	8	1.27 (0.68-2.37)
			Anorectal	263	LUTS		4.01 (2.11-7.62)
			Anorectal	263	Male		1.49 (0.83-2.67)
Lin[38]	2010	Case-Control	Haemorr.	467	Age >55	7	0.77 (0.45-1.33)
			Haemorr.	467	Male		1.22 (0.82-1.82)
Prasad[39]	1978	Prospective	Anorectal	620	Age >50	7	2.52 (0.30-21.5)
			Anorectal	620	Male		0.90 (0.20-4.06)
Toyonaga[40]	2006	Case-Control	Anorectal	2011	Age >50	6	1.56 (1.23-1.98)
			Anorectal	2011	LUTS		2.19 (1.55-3.11)
			Anorectal	2011	Male		0.33 (0.26-0.41)
			Anorectal	2011	Diabetes		2.09 (1.15-3.78)
Kozol[41]	1992	Prospective	IH	113	Age >60	7	4.00 (1.15-13.9)
			IH	113	LUTS		2.22 (0.70-7.02)
Koch[8]	2006	Case-Control	IH	68	BPH	6	1.17 (0.39-3.51)
			IH	68	Prostate Cancer		1.00 (0.19 to 5.34)
			IH	68	Previous Urinary Retention		0.56 (0.12-2.56)
Sivasankaran[42]	2014	Case-Control	IH	339	BPH	6	11.5 (4.75-27.6)
			IH	339	Prostate Cancer		3.97 (1.19-13.23)
			IH	350	Male		2.19 (0.13-38.02)
			IH	350	Diabetes		0.58 (0.21-1.56)
Sanjay[43]	2006	Case-Control	IH	577	ASA 3 and 4	5	6.75 (1.30-35.17)
Hewitt[44]	1996	Case-Control	Hemorr.	57	HIV infection	8	0.41 (0.09-1.78)
Iramaneerat[45]	2013	Case-Control	Anorectal	245	Male	6	0.50 (0.26-0.95)
Kiyak[46]	2009	Prospective	Spincterotomy	129	Male	7	2.14 (0.86-5.32)
Lau[47]	2002	Case-Control	IH	300	Male	6	1.04 (0.06-18.60)
Zack[48]	1962	Prospective	Anorectal	212	Male	6	1.20 (0.69-2.11)

Abbreviations: CI- confidence interval; RCT- randomized controlled trial; IH- inguinal herniorrhaphy; Hemorr.- hemorrhoidectomy.
[a]Jadad and Newcastle-Ottawa scores for randomized and non-randomized trials respectively

Table 1 – design, clinical characteristics, risk factors and quality assessment of the twenty-one included studies.

Identification

Electronic bibliographies
n=3714

Hand-searching
n=45

Screening

Studies for abstract review
n=3759

Reasons for exclusion (n=3189):
- Inappropriate procedure or study design (n=2926)
- Systematic review (n=263)

Eligibility

Manuscripts retrieved for review
n=570

Reasons for exclusion (n=549):
- Unsuitable risk factors (n=256)
- Unsuitable study design (n=174)
- Unsuitable procedure (n=98)
- Patient age <16 (n=12)
- Inadequate data (n=9)

Included

Studies for inclusion (n=21):
- RCT (4)
- Prospective cohort (7)
- Case-control (10)

Author(s) and Year		Odds Ratio [95% CI]
Zack et al., 1962		1.20 [0.69 , 2.11]
Prasad and Abcarian, 1978		0.90 [0.20 , 4.06]
Eftaiha et al., 1980		1.49 [0.83 , 2.67]
Zaheer et al., 1998		1.23 [0.87 , 1.75]
Lau et al., 2002		1.04 [0.06 , 18.60]
Toyonaga et al., 2006		0.33 [0.26 , 0.41]
Kiyak et al., 2009		2.14 [0.86 , 5.32]
Lin et al., 2009		1.22 [0.82 , 1.82]
Iramaneerat and Yongpradit, 2013		0.50 [0.26 , 0.95]
Sivasankaran et al., 2014		2.19 [0.13 , 38.02]
Random Effects Model		0.96 [0.62 , 1.50]

0.05   0.25   1.00   4.00   20.00

Heterogeneity

Q Score = 74.2, p<0.0001 (9 d.f.)

I^2 = 82%

Odds Ratio (log scale)

Author(s) and Year	Age Cut−Off (yrs)		Odds Ratio [95% CI]
Zaheer et al., 1998	47		2.30 [1.07 , 4.93]
Prasad and Abcarian, 1978	50		2.52 [0.30 , 21.48]
Toyonaga et al., 2006	50		1.56 [1.23 , 1.98]
Eftaiha et al., 1980	55		1.27 [0.68 , 2.37]
Zaheer et al., 1998	55		1.25 [0.82 , 1.91]
Lin et al., 2010	55		0.77 [0.45 , 1.33]
Kozol et al., 1992	60		4.00 [1.15 , 13.91]
Beltran and Cruces, 2006	70		12.43 [5.96 , 25.94]
Amato et al., 2012	70		3.34 [0.37 , 30.42]
Random Effects Model			2.11 [1.15 , 3.86]

0.05   0.25   1.00   4.00   20.00

Heterogeneity

Q Score = 42.2, p<0.001 (8 d.f.)

I^2 = 81%

Odds Ratio (log scale)

Age Cut−Off (yrs)	No. of Studies		Random Effects Model Odds Ratio [95% CI]
Age ≥50	8		2.11 [1.06 , 4.21]
Age ≥55	6		2.25 [0.92 , 5.53]
Age ≥60	3		7.09 [2.79 , 18.03]

0.25   1.00   4.00   20.00   100.00

Odds Ratio (log scale)

Author(s) and Year   **Odds Ratio [95% CI]**

Eftaiha et al., 1980   4.01 [2.11 , 7.62]
Kozol et al., 1992   2.22 [0.70 , 7.02]
Zaheer et al., 1998   1.85 [1.04 , 3.30]
Toyanaga et al., 2006   2.19 [1.55 , 3.11]
Koch et al., 2006   1.17 [0.39 , 3.51]
Sivasankaran et al., 2014   11.45 [4.75 , 27.58]

Random Effects Model   2.83 [1.57 , 5.08]

Heterogeneity   0.05   0.25   1.00   4.00   20.00
Q Score = 17.0, p = 0.005 (5 d.f.)
I^2 = 77%   Odds Ratio (log scale)

Q Score = 6.45, p = 0.17 (4 d.f.)

I^2 = 23%

Author(s) and Year	Odds Ratio [95% CI]
Goldman et al., 1988	0.06 [0.00 , 1.14]
Cataldo and Senagore, 1991	0.67 [0.22 , 2.07]
Woo and Camalt, 1995	5.00 [0.23 , 108.01]
Gonullu et al., 1999	0.23 [0.06 , 0.87]
Mohammadi–Fallah et al., 2012	0.15 [0.02 , 1.27]
Random Effects Model	0.37 [0.15 , 0.91]

Heterogeneity

0.05   0.25   1.00   4.00   20.00

Odds Ratio (log scale)