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Patient- and tumour-related prognostic factors for urinary incontinence after radical prostatectomy for non-metastatic prostate cancer: A systematic review and meta-analysis

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Abstract

Context: Whilst urinary incontinence (UI) commonly occurs after radical prostatectomy (RP), it is unclear which factors increase its risk of development.

Objective: To perform a systematic review on patient- and tumour-related prognostic factors for post-RP UI. The primary outcome was post-operative UI within 3 months; secondary outcomes included UI at 3-12 months and ≥12 months, post-operatively.

Evidence acquisition: Databases including Medline, EMBASE and CENTRAL were searched between January 1990-May 2020. All studies reporting patient- and tumour-related prognostic factors in uni/multivariable analysis were included. Surgical factors were excluded. Risk of bias (RoB) and confounding assessments were performed using QUIPS. Random effects meta-analyses were performed for all prognostic factor, where possible.

Evidence synthesis: 119 studies (5 RCTs, 24 prospective, 88 retrospective and 2 case-control studies) with 131,379 patients were included. RoB was high for study participation and confounding; moderate to high for statistical analysis, study attrition, and prognostic factor measurement; and low for outcome measurements. Significant prognostic factors for post-operative UI within 3 months were age (OR per yearly increase: 1.04, 95% CI 1.03 – 1.05), membranous urethral length (MUL) (OR per increase in mm: 0.81, 95% CI 0.74 – 0.88), prostate volume (PV) (OR per increase in ml: 1.005, 95% CI: 1.000 – 1.011) and Charlson Comorbidity Index (CCI) (OR: 1.28, 95% CI 1.09-1.50).

Conclusions: Increasing age, shorter MUL, larger PV and higher CCI are independent prognostic factors for UI within 3 months after RP, with all except CCI remaining prognostic at 3-12 months.

Patient summary: We reviewed the literature to identify patient and disease factors associated with urinary incontinence after surgery for prostate cancer. We found increasing age, larger prostate volume, shorter length of a section of the urethra (membranous urethra) and reduced fitness were associated with worse urinary incontinence for the first 3 months after surgery, with all except reduced fitness remaining prognostic at 3-12 months.

1. INTRODUCTION

One of the commonest first-line treatments offered to men with non-metastatic prostate cancer (PCa) is radical prostatectomy (RP). Urinary incontinence (UI) is one of the functional complications. The rate of UI based on a 'no pad' definition at 12 months ranges from 4-31%[1]. This heterogeneity in reported post-operative UI rate, is likely related to multiple pre-, intra- and post-operative factors[2], both at the patient and surgeon level[3]. Unfortunately, there is limited understanding about these risk factors.

Research to identify and quantify the impact of these risk factors is supported by a recent consensus report from International Consultation on Incontinence-Research Society (ICI-RS)[4] and is important to ensure informed consent for surgery.

The primary objective of this SR was to identify patient- and tumour-related prognostic factors for postoperative UI within 3 months after RP for non-metastatic PCa, while the secondary objective was to identify prognostic factors between 3-12 months and >12 months after RP.

2. EVIDENCE ACQUISITION

The review was commissioned and undertaken by the European Association of Urology (EAU) PCa Guideline Panel as part of its guideline update for 2021. The protocol for this review has been published (http://www.crd.york.ac.uk/PROSPERO; CRD42020186524). Briefly, the review was performed according to PRISMA guidelines[5] and Cochrane review principles[6]. English language articles published from January 1990 to May 2020 were included. Appendix A includes full details of the search strategies used. All abstracts and resulting full-text articles were independently screened and data extraction was performed in duplicate (ML, NG, FZ, MC, CB) and disagreement was resolved by discussion or reference to an independent third party (TVDB).

All types of studies exclusively investigating patient- and tumour-related prognostic factors for postoperative UI in a uni- or multivariable analysis were included. All surgical-related factors were excluded. The study population was limited to men with histologically proven non-metastatic PCa who underwent RP by all routes (transperitoneal/ retropubic, Retzius sparing, transperineal) and approaches (open,

laparoscopic, robot-assisted), irrespective of whether they had pre-operative UI/LUTS or were offered lymph node dissection or neo-adjuvant therapy. Due to expected clinical heterogeneity, all UI definitions were included. Sensitivity and sub-group analyses were planned to assess the potential impact of heterogeneity in UI definitions.

Risk of bias (RoB) was assessed using the Quality In Prognosis Studies (QUIPS) tool[7], as recommended by the Cochrane Prognosis Methods Group. The confounding factors considered were clinical T stage, biopsy Gleason score, age, BMI, comorbidities, and adjuvant therapies. To evaluate whether adjusted results were prone to small study effects (e.g. arising from publication bias), funnel plots were generated, and Egger's test was performed to evaluate the presence of asymmetry.

Where necessary, we imputed missing standard errors from reported P-values or 95% confidence intervals (CIs), and unadjusted odds ratios (OR) were calculated from reported counts where possible. Forest plots were generated to visualize the extracted effects of each possible prognostic factor. We adopted a three-level random effects model using restricted maximum likelihood estimation to obtain a summary estimate of the prognostic effect. This multilevel meta-analysis approach is appropriate to account for potential between-study heterogeneity and for non-independence between multiple results from the same study (e.g. studies reporting an OR at multiple time points). We quantified the presence of statistical heterogeneity using I^2 and prediction intervals. Briefly, I^2 is a measure of the consistency among confidence intervals of primary studies, and ranges from 0% (no heterogeneity) to 100% (excessive heterogeneity)[8]. Conversely, the prediction interval (PI) provides a range for the true prognostic effect across study settings[9]. A Student-T distribution was used to derive 95% CIs and PIs. Finally, we performed three-level meta-regression analyses to investigate whether the effect of the prognostic factors was affected by the time between RP and the assessment of UI (expressed as total number of months after RP), or by the adopted UI definition. Meta-regression is loosely related to linear regression but incorporates meta-analysis principles to determine the contribution of each study[10]. All pooled analyses were performed using the rma.mv function in the R package metafor.

3. EVIDENCE SYNTHESIS

3.1. Quantity of evidence identified

The study selection process is outlined in the PRISMA flow diagram (Fig. 1). 5985 records were identified, and 3752 were screened after removal of duplicates. Of these, 329 articles were eligible for full-text screening. Finally, 119 studies met the inclusion criteria.

3.2. Characteristics of the included studies

The 119 included studies recruited 131,379 patients, including 5 randomized controlled trials (RCTs)[11-15] and 114 nonrandomized studies (NRSs; 24 prospective cohorts[16-39], 88 retrospective cohorts[40-127] and 2 case control studies[128, 129]). Seven different UI definitions were used including: ≥1 pads/day (including safety pads) in 47 studies, >1 pad/day in 45 studies, any self-reported urinary leakage or urinary leakage as an answer to validated questionnaires (e.g. EPIC-26, ICIQ-SF) in 15 studies, combination of pad use and self-reported urinary leakage in 5 studies, weight of urine loss (≥1 gr/hour; >2-20 gr/day) in 3 studies, use of any protection in 2 studies and treatment with surgical procedure for UI in 1 study (definition not reported in 1 study). Robot-assisted, open, and laparoscopic approach was used in 51, 25 and 10 studies respectively, while in 32 studies the previous approaches were combined (approach not reported in 1 study) (Appendix B). Supplementary Table 1 presents the baseline characteristics of included studies.

3.3. Risk of bias and confounding assessment of included studies

Figure 2 and Supplementary Figure 1 summarize the QUIPS-based RoB assessment of all studies. Overall, there was high RoB for the domains of study participation and study confounding, as in most studies inclusion and exclusion criteria were not adequately described and confounding factors were not adequately considered through statistical adjustments. Statistical analysis was judged to be either moderate or high RoB for the vast majority of studies (>75%), as in some studies, it was not clear whether OR were reported for UI or continence and the unit of analysis was not always clear. Study attrition and prognostic factor measurement were judged to be moderate to high RoB in >50% of included studies, while outcome measurement was judged to be low RoB in a significant proportion of included studies (>65%). Finally, Egger's test showed significant funnel plot asymmetry (i.e. presence of small study effects) for studies reporting adjusted results for age >12 months after RP and for studies reporting adjusted results for MUL (funnel plots in Appendix C).

3.4. Results of evidence synthesis

3.4.1. Patient-related prognostic factors for UI

Below we summarize results for the potential patient-related prognostic factors that were reported most frequently in the included studies (Supplementary Table 2).

3.4.1. 1. Age

A total of 108 studies investigated whether age was associated with UI after RP. The age distribution across studies is presented in Supplementary Figure 2. We extracted unadjusted (univariable) and adjusted (multivariable) association between this prognostic factor and postoperative UI. Results of the studies reporting an unadjusted association are presented in Supplementary Figure 3.

Thirty-seven, 36 and 11 studies reported multivariable analysis (MVA) for age within 3, 3-12 and >12 months after RP, respectively (Figures 3a, b and Supplementary Figure 4a). The pooled OR for age within 3, 3-12 and >12 months after RP were 1.04 (95% CI 1.03 – 1.05), 1.03 (95% CI 1.02-1.05) and 1.04 (95% CI 1.02-1.07) per increment in year respectively, indicating that older patients have an increased risk of incontinence. Supplementary Figure 4b presents the meta-regression analysis, for studies reporting MVA for age as a continuous variable. Here, we did not find any evidence that the prognostic effect of age is related to the time between RP and assessment of UI (slope for log OR = 0.0004, p = 0.17). Finally, thirteen studies analyzed age as a categorical variable, often using a cut-off around 65 years (Supplementary Figure 5a-c). Also, for these studies, we found that older patients have an increased risk of incontinence. We subsequently performed a meta-regression on studies which analysed age as a continuous variable (as more studies reported on it) to investigate if the prognostic effect of age varies by UI definition (Supplementary Figure 6a-c) but did not find any evidence to support this hypothesis.

Overall, results from the three-level random effects meta-analysis and meta-regression models indicate that increased age is a risk factor for incontinence after RP, irrespective of UI definition.

3.4.1.2. Membranous urethral length (MUL)

Twenty-six studies examined the association of MUL and postoperative UI. In all but two studies included, MUL was measured by magnetic resonance imaging (MRI). In most studies MUL was defined as the distance from the prostatic apex to the level of the urethra at the penile bulb, measured via T2-weighted MRI images on coronal, sagittal view, or both. Results of the studies reporting a univariable analysis are presented in Supplementary Figure 7, while the MUL distribution across studies is presented in Supplementary Figure 8 (mean MUL measurements reported across included studies ranged from 10.4 to 15.9 mm).

Nine and 10 studies reported adjusted OR for MUL within 3 and 3-12 months after RP. The pooled OR for MUL within 3 and 3-12 months after RP were 0.81 (95% CI 0.74 – 0.88) and 0.83 (95% CI 0.76-0.91) per increment in mm (Figure 4a, b), indicating that patients with longer MUL have a decreased risk of incontinence. Only one study reported MVA for MUL later than 12 months after RP (OR 0.64, 95% CI 0.56-0.73) (Supplementary Figure 9a). Using meta-regression on studies which analysed MUL as a continuous variable, we found that the adjusted log OR for MUL further decreases as the time between RP and assessment of UI increases (slope = -0.0058, P value = 0.02) (Supplementary Figure 9b). Finally, five studies analyzed MUL as a categorical variable (Supplementary Figure 10), concluding that patients with longer MUL seemed to have a decreased risk of incontinence. Sensitivity analyses using meta-regression could not establish any relation between the prognostic effect of MUL and UI definition (Supplementary Figure 11a, b).

Results from the random effects meta-analysis and meta-regression models indicated patients with longer MUL have higher probability of continence after RP, irrespective of UI definition.

3.4.1.3. Body mass index (BMI)

The association of BMI and postoperative UI was examined in 55 studies. Results of the studies reporting a univariable analysis are presented in Supplementary Figure 12, and studies reporting multivariable analysis for categorized values of BMI are presented in Supplementary Figure 13. The BMI distribution across studies is presented in Supplementary Figure 14.

The adjusted OR for BMI as a continuous variable within 3, 3-12 and >12 months after RP were reported in 16, 14 and 4 studies respectively (Supplementary Figure 15a-c).

The pooled OR within 3, 3-12 and >12 months after RP were 0.99 (95% CI 0.96 – 1.03), 1.01 (95% CI 0.99-1.04) and 1.04 (95% CI 0.95-1.14) respectively. There was no evidence that the log OR for BMI was affected by the time between RP and assessment of UI (slope = 0.0001, P = 0.85) (Supplementary Figure 15d).

Results from the random effects meta-analysis and meta-regression models suggest that BMI does not meaningfully affect the risk of postoperative UI.

3.4.1.4. Pre-operative Lower Urinary Tract Symptoms (LUTS)

We analysed 14 studies that used the International Prostate Symptom Score (IPSS) tool to assess the association with UI. Results of the studies reporting univariable and multivariable analysis are presented in Supplementary Figure 16 and 17, respectively.

Overall, the available data was inconclusive, and their synthesis could not confirm a relationship between pre-operative IPSS and postoperative UI for the first 12 months after surgery.

3.4.1.5. Prostate volume (PV)

Forty-eight studies examined the association of PV and postoperative UI. Results of the studies reporting a univariable analysis are presented in Supplementary Figure 18, while the PV distribution across studies is presented in Supplementary Figure 19.

The adjusted OR for PV (in ml) within 3, 3-12 and >12 months after RP were reported in 16, 18 and 3 studies, respectively (Figure 5a, b and Supplementary Figure 20a). The pooled OR within 3, 3-12 and >12 months after RP were 1.005 (95% CI 1.000 – 1.011), 1.004 (95% CI 1.000-1.008) and 1.001 (95% CI 0.996-1.005) per increment in ml. These results were unaffected by the time between RP and assessment of UI (slope = 0.00, P = 0.65) (Supplementary Figure 20b), or by the adopted UI definition (Supplementary figure 21a-c).

Overall, results from the random effects meta-analysis and meta-regression models suggest that the risk of postoperative UI increases for patients with larger PV for the first 12 months after surgery.

3.4.1.6. Charlson comorbidity index (CCI) score

Eleven studies examined the association of CCI score and postoperative UI. Results of the studies reporting a univariable analysis are presented in Supplementary Figure 22.

MVA for CCI within 3 months after RP was reported in 4 studies as a categorical variable (Figure 6a). The pooled OR was 1.28 (95% CI 1.09-1.50). MVA for CCI between 3 and 12 months after RP was reported in 6 studies (in 2 as a continuous variable and in 4 as a categorical value). The pooled OR was 1.01 (95% CI 0.59-1.70) for studies reporting CCI as a continuous variable (Figure 6b) and 1.29 (95% CI 0.95-1.77) for studies reporting CCI as a categorical variable with CCI=0 as reference (Figure 6c). There was only 1 study reporting MVA for CCI later than 12 months after RP (Supplementary Figure 23). Overall, although the available data were very imprecise, their synthesis suggests that CCI is related to postoperative UI, only for the first 3 months after surgery.

3.4.2. Tumour-related prognostic factors for UI

Below we summarize results for the potential tumour-related prognostic factors that were reported most frequently in the included studies (Supplementary Table 2)

3.4.2.1. Preoperative PSA

Forty-eight studies investigated the association between preoperative PSA and postoperative UI. Results of the studies reporting univariable and multivariable analysis are presented in Supplementary Figure 24 and 25, respectively.

Results from the random effects meta-analysis and meta-regression models suggest that preoperative PSA does not meaningfully affect the risk of postoperative UI.

3.4.2.2. Biopsy Gleason score (bGS)

We identified 22 studies investigating bGS association with postoperative UI. Results of the studies reporting univariable and multivariable analysis are presented in Supplementary Figure 26 and 27, respectively.

The random effects meta-analysis and meta-regression models could not determine whether bGS affects the risk of postoperative UI.

3.4.2.3. Clinical T stage (cT)

The relationship of cT stage and postoperative UI was examined in 11 studies. Results of the studies reporting univariable and multivariable analysis are presented in Supplementary Figure 28 and 29, respectively.

Overall, the random effects meta-analysis and meta-regression models could not determine whether cT stage meaningfully affects the risk of postoperative UI.

3.5. Discussion

3.5.1. Principal findings

The current review synthesizes the existing evidence regarding which patient and tumour characteristics are associated with UI in men treated with RP for non-metastatic PCa. We primarily focused on summarizing the results from MVA, as suggested when conducting an SR of prognostic factors[130]. Due to the plethora of prognostic factors for UI reported in the literature, we performed a meta-analysis for those factors that were most frequently reported in the included studies. These factors were rarely adjusted for the same set of other prognostic factors, which is not ideal[130]; therefore a random effects approach was utilised to account for any heterogeneity across studies. We also examined unadjusted results for possible prognostic factors and found similar results. Based on these analyses, in patients who underwent RP as primary treatment for PCa, we found evidence that four patient-related factors were meaningfully associated with postoperative UI, regardless of the used definition of UI.

Age has been previously reported as a prognostic factor for UI[1], while also included as one of the variables in tools used for the prediction of UI[63, 81, 131]. Our meta-analysis confirms the prognostic role of age, irrespective of time between RP and UI, and irrespective of UI definition. For instance, the pooled adjusted OR for age between 3 and 12 months after RP was 1.03 per increment in year, which means that the odds for UI increases by approximately 3% and 15% for every 1- and 5-year increase in age, respectively.

The second factor that we found to be significantly associated with a return to continence in men following RP, irrespective of UI definition, was preoperative MUL. In our meta-analysis the pooled adjusted OR for MUL between 3 and 12 months after RP was 0.83, which means that the odds for UI decreases by approximately 17% for every 1 mm increase in MUL length for that period. Meta-regression results suggest that the adjusted log OR for MUL further decreases as the time between RP and assessment of UI increases, however, there is lack of data beyond the first year after RP. Our results are consistent with the results of a recent SR that investigated preoperative MUL as a prognostic risk factor for UI[132]. In this SR, the mean MUL

measurements reported across all studies ranged from 10.4 to 14.5 mm (however, individual measurements ranged from 5-34.3 mm). Our results also support the use of MUL as a variable in the development of predictive models for continence recovery after RP[63, 81].

The third factor we found to have a prognostic value for return to continence for the first 12 months after RP was PV. In our meta-analysis the pooled adjusted OR for PV was 1.005 within 3 months after RP and 1.004 for the period between 3 and 12 months, per increment in ml. These results imply that the odds for UI increases by 5% for the first 3 months and 4% for 3 to 12 months after RP, for every 10 ml increase in PV. However, the prognostic effect of PV was prone to substantial clinical heterogeneity, with prediction interva15.ls indicating that increasing PV can also decrease the risk of UI in certain populations. A potential reason for this heterogeneity was the variability in measuring PV, with the majority of studies in our review not defining how PV was measured.

Finally, most studies reporting on comorbidities investigated the role of CCI in postoperative UI. Our results suggest that for the first 3 months after RP, higher CCI score increases the odds for UI, however this effect could not be confirmed for UI >3 months after RP.

Regarding the role of other patient-related factors, we found no evidence that BMI is meaningfully associated with postoperative UI, as previously suggested by other reviews[1, 133], while there was a lack of data to draw any conclusions about the role of IPSS. Concerning tumour-related factors, there were insufficient data available to draw any conclusions for the role of bGS and cT stage, while we found no association between preoperative PSA and postoperative UI.

3.5.2. Implications for clinical practice and further research

Determining the appropriate treatment choice for patients with non-metastatic PCa remains a challenge, especially in view of possible adverse functional outcomes impairing patients' quality of life. UI remains one of the major complications following RP. Informed patient counselling requires accurate prognostic information. The implication of our findings is that patients with a combination of the 4 prognostic factors (older and unfit patients with shorter MUL and larger prostate volume) have a significantly higher risk of developing post-operative UI, and hence should be

counselled accordingly. This may prompt patients to either opt for other forms of therapy or have more realistic expectations regarding their post-operative continence status. Age, MUL, PV and CCI can therefore be used to guide risk stratification in clinical practice; however, other factors may also be also important (eg. surgical factors)[133, 134].

In our meta-analysis estimates of interest were obtained from individual studies and then combined into a weighted average. This method is prone to several limitations and cannot directly be used to define an absolute threshold for factors found to be prognostic. A meta-analysis of individual participant data (IPD) could help to further resolve possible sources of between-study heterogeneity[135, 136], and to develop a prediction model for risk stratification in patients undergoing RP.

3.5.3. Limitations and strengths of this SR

One of the main strengths of this SR, is that it was developed and conducted by a multidisciplinary panel of experts (EAU Prostate Cancer Guidelines Panel) supported by a methodology team (EAU Guidelines Office Methods Committee). The review has been performed robustly in accordance with recognized standards.

Limitations include the retrospective nature of the majority of included studies resulting in moderate to high RoB and confounding, their sometimes poor quality of reporting (frequently not clearly indicating whether results were derived for UI or continence), the substantial heterogeneity in design and analysis choices (e.g. inconsistent choice of UI definitions, method of measurement, analysis strategies, etc), the lack of data for other potential prognostic factors (e.g. risk groups), and finally the overall clinical and methodological differences across studies. Many studies were prone to selective reporting, and only presented (notably adjusted) OR when statistically significant. Funnel plot inspection confirmed the potential presence of publication bias for studies reporting adjusted results for age >12 months after RP and for MUL for <3 months and 3-12 months post-operatively. We acknowledge that adjuvant therapy may have affected the development of UI in some patients, thereby confounding the results. However, the vast majority of included studies did not specify any adjuvant therapy for recruited patients, and hence we believe the risk of confounding for this variable was low. Furthermore, interobserver variability in the assessment of MUL is untested and might be high. Thus, interpretation of data presented in this SR should be performed

cautiously. For evidence that could further guide clinical practice, access to IPD would be the ideal next step. To this end, the EAU Guidelines Office has established the PIONEER consortium with the purpose of combining high quality data from large organizations across different countries. Finally, UI related factors such as surgical/technical [133] were not included in our SR. Variation in surgical/technical factors may have contributed to the high degree of statistical heterogeneity encountered, and our findings may have been confounded by these factors. Analysing these factors is beyond the scope of our review, nevertheless during patient counselling and for identifying patients at high risk of UI, all these factors should be considered.

4. CONCLUSION

Based on our SR, we found in patients who underwent RP as primary treatment, the main prognostic factors influencing the development of UI were increasing age, shorter MUL and, to a limited extent, larger PV. These factors were meaningfully associated with postoperative UI for at least 12 months after surgery. Higher CCI score was also associated with increased risk of UI but this was only demonstrated for the first 3 months post-operatively. PSA and BMI were not meaningfully related to UI, while due to the lack of available data, we could not draw any conclusions for bGS, cT stage and IPSS. These findings can guide and inform clinicians and patients in treatment decision-making, and guide further research, especially in the development of prognostic models and nomograms which can estimate the absolute risk of UI after RP in individual patients.

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