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EDITORIAL
IN THIS ISSUE

Urethroplasty is highlighted in the first number of 2023 in International Brazilian Journal of Urology

Luciano A. Favorito [1, 2]

[1] *Unidade de Pesquisa Urogenital - Universidade do Estado do Rio de Janeiro - Uerj, Rio de Janeiro, RJ, Brasil,*
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The January-February number of Int Braz J Urol is the 20th under my supervision. In this number the Int Braz J Urol presents original contributions with a lot of interesting papers in different fields: Urethroplasty, SARS-CoV-19, Robotic Surgery, Prostate Cancer, Bladder Cancer, LUTS, Renal Cancer, Reconstructive urology and Renal stones. The papers came from many different countries such as Brazil, China, USA, Japan and UK, and as usual the editor´s comment highlights some of them. The editor in chief would like to highlight the following works:

Dr. Ma and collegues from China, presented in page 8 (1) a nice systematic review about the smoking and stricture recurrence after urethroplasty and concluded that smoking can increase stricture recurrence risk after the urethroplasty and suggested that quitting smoking may be a good option for patients undergoing urethroplasty surgery.

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CONFLICT OF INTEREST

None declared.

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INTERNATIONAL
BRAZ J UROL

CONSULTING EDITORS

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EDITORIAL

The best reviewers of International Brazilian Journal of Urology in 2022

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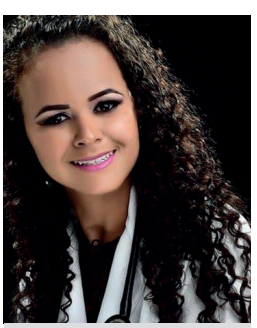
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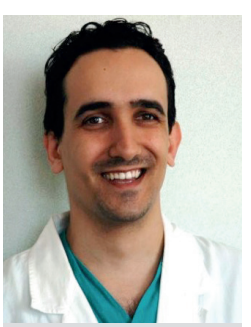
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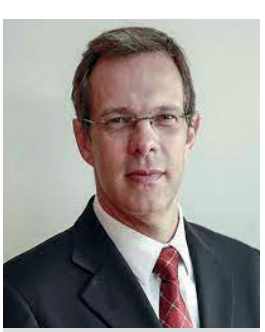
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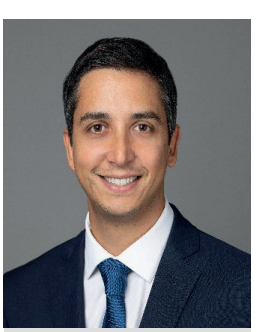
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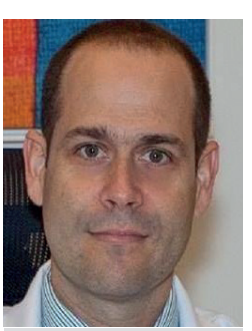
Renato N. Pedro


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EDITORIAL

Selection of best videos of the year for 2022

Philippe E. Spiess [1, 2]

[1] Department of GU Oncology Moffitt Cancer Center, FL, USA; [2] Department of Tumor Biology Moffitt Cancer Center, FL, USA

COMMENT

Dear readers,

It is a distinct pleasure to once again highlight the significant contributions made to the International Brazilian Journal of Urology over the past year. Our journal has continued to expand its global reputation and broad readership over a tumultuous period of a global pandemic and diverse world conflicts as well as challenges. It is a true testament to the commitment of our journal and contributors to forge through in advancing science and surgical innovation during these times, with a direct consequence of this being an increasing recognition of our journal among the top tiered urological journals which is so very well depicted by our rapidly rising impact factor now benchmarked with many of the very best in our field.

In making the selection of best videos of the year, several criteria have been employed including their surgical novelty and potential to improve patient care. These are clearly high bars set but truthfully I am thrilled to report that these challenging criteria have been achieved to a large extent by many of our published videos so all contributing authors of accepted videos over the past year are to be congratulated nevertheless there can only be a few select winners and on that note, I am pleased to announce that the first prize for best video of the year is awarded to the submission by Moschovas MC et al. entitled "Da Vinci SP radical prostatectomy: A multicentric collaboration and step-by-step techniques" published in the July-August issue (Vol 48(4):728-729) of our journal (1). The video provides a very practical approach to conducting minimally invasive radical prostatectomy using a single port platform as defined by some of the premier global surgical leaders in this milieu. The authors are applauded for sharing their wealth of knowledge and technical refinements in making this surgical approach highly accessible to many surgeons seeking to offer this surgical modality within their patient population. The second prize is awarded to Inzillo R et al. from the department of Urology from Guastalla Hospital from Emilia-Romagna, Italy for their video entitled "Percutaneous and endoscopic combined treatment of bladder and renal lithiasis in Mitrofanoff conduit" which was published in our May-June issue (Vol48(3)598-599) (2). As nicely detailed by the authors, the significant benefits to adopting a purely endoscopic management in managing bladder and renal calculi in patients with a Mitrofanoff conduit cannot be overemphasized. A very well strategized and performed surgical approach is demonstrated which can serve as a framework for colleagues managing such patients to consider

and potentially adopt, with remarkable benefits offered to patients in doing so in terms of quicker recovery and decreased potential surgical morbidity. The third prize is awarded to the video publication by Grosso AA et al. entitled "Three-dimensional reconstruction and intraoperative ultrasonography: Crucial tools to safely approach highly complex renal masses" from the department of experimental and clinical medicine, University of Florence in Italy which was published in our November-December issue (Vol 48(6):996-997) (3). This video is a beautiful depiction on how novel imaging tools (both pre- and intra-operative) can be employed and integrated as powerful tools to not only guide but refine our surgical approach to highly complex renal masses being managed using minimally invasive techniques in the completion of nephron sparing surgery. This is becoming an increasingly frequent surgical case type completed by many urologists and urologic oncologists throughout the world hence the implications of this work are significant with this video providing a nice overview on how this can be done seamlessly in day-to-day practice.

In my closing remarks, I would like to thank our dedicated readers and submitting contributors in allowing our journal to achieving new echelons of global recognition within the urological community and we are very excited in envisioning the promising future ahead.

Warmest regards and best wishes,

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CONFLICT OF INTEREST

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VIDEO SECTION

LETTER TO THE EDITOR

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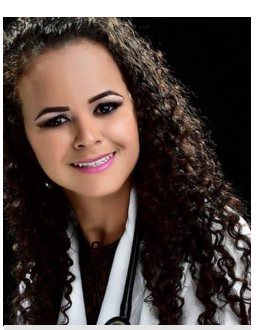

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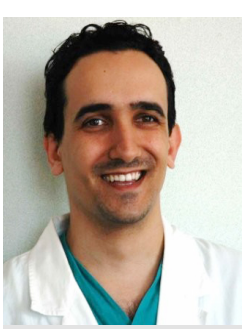

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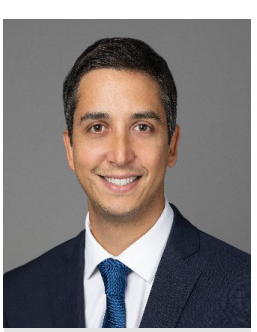

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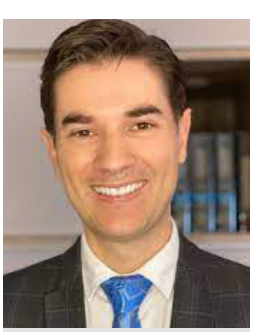

Márcio A. Averbeck

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[1] Department of GU Oncology Moffitt Cancer Center, FL, USA; [2] Department of Tumor Biology Moffitt Cancer Center, FL, USA

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Dear readers,

It is a distinct pleasure to once again highlight the significant contributions made to the International Brazilian Journal of Urology over the past year. Our journal has continued to expand its global reputation and broad readership over a tumultuous period of a global pandemic and diverse world conflicts as well as challenges. It is a true testament to the commitment of our journal and contributors to forge through in advancing science and surgical innovation during these times, with a direct consequence of this being an increasing recognition of our journal among the top tiered urological journals which is so very well depicted by our rapidly rising impact factor now benchmarked with many of the very best in our field.

In making the selection of best videos of the year, several criteria have been employed including their surgical novelty and potential to improve patient care. These are clearly high bars set but truthfully I am thrilled to report that these challenging criteria have been achieved to a large extent by many of our published videos so all contributing authors of accepted videos over the past year are to be congratulated nevertheless there can only be a few select winners and on that note, I am pleased to announce that the first prize for best video of the year is awarded to the submission by Moschovas MC et al. entitled "Da Vinci SP radical prostatectomy: A multicentric collaboration and step-by-step techniques" published in the July-August issue (Vol 48(4):728-729) of our journal (1). The video provides a very practical approach to conducting minimally invasive radical prostatectomy using a single port platform as defined by some of the premier global surgical leaders in this milieu. The authors are applauded for sharing their wealth of knowledge and technical refinements in making this surgical approach highly accessible to many surgeons seeking to offer this surgical modality within their patient population. The second prize is awarded to Inzillo R et al. from the department of Urology from Guastalla Hospital from Emilia-Romagna, Italy for their video entitled "Percutaneous and endoscopic combined treatment of bladder and renal lithiasis in Mitrofanoff conduit" which was published in our May-June issue (Vol48(3)598-599) (2). As nicely detailed by the authors, the significant benefits to adopting a purely endoscopic management in managing bladder and renal calculi in patients with a Mitrofanoff conduit cannot be overemphasized. A very well strategized and performed surgical approach is demonstrated which can serve as a framework for colleagues managing such patients to consider

and potentially adopt, with remarkable benefits offered to patients in doing so in terms of quicker recovery and decreased potential surgical morbidity. The third prize is awarded to the video publication by Grosso AA et al. entitled "Three-dimensional reconstruction and intraoperative ultrasonography: Crucial tools to safely approach highly complex renal masses" from the department of experimental and clinical medicine, University of Florence in Italy which was published in our November-December issue (Vol 48(6):996-997) (3). This video is a beautiful depiction on how novel imaging tools (both pre- and intra-operative) can be employed and integrated as powerful tools to not only guide but refine our surgical approach to highly complex renal masses being managed using minimally invasive techniques in the completion of nephron sparing surgery. This is becoming an increasingly frequent surgical case type completed by many urologists and urologic oncologists throughout the world hence the implications of this work are significant with this video providing a nice overview on how this can be done seamlessly in day-to-day practice.

In my closing remarks, I would like to thank our dedicated readers and submitting contributors in allowing our journal to achieving new echelons of global recognition within the urological community and we are very excited in envisioning the promising future ahead.

Warmest regards and best wishes,

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ARTICLE INFO

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REVIEW ARTICLE

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Smoking is an independent risk factor for stricture recurrence after the urethroplasty: a systematic review and meta-analysis

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ABSTRACT

Objective: To clarify the association between smoking and stricture recurrence after urethroplasty.

Materials and Methods: Pubmed, Web of Science, Embase, and Cochrane databases were searched with keywords: "urethroplasty," "buccal mucosa graft urethroplasty," "oral mucosa graft urethroplasty," "excision and primary anastomosis urethroplasty," "urethral stricture recurrence" until July 1, 2022. Inclusion and exclusion criteria were based on PICOS principles. The quality of included studies was assessed by Newcastle--Ottawa Scale (N.O.S.) system. Hazard ratio (H.R.), odds ratio (OR), and relative risk (RR) with 95% confidence interval (CI) were extracted or re-calculated from included studies. Meta-analysis was performed with Stata 15.0 based on univariate and multivariate data separately. Sensitivity analysis was performed to test the stability of the meta-analysis. I2 was calculated to evaluate heterogeneity. Publication biases were assessed by Egger's and Begg's tests. Funnel plots of univariate analysis and multivariate analysis were also offered.

Results: Twenty one studies with 6791 patients were involved in this meta-analysis. The analysis results of the two stages were consistent. In the univariate meta-analysis stage, 18 studies with 5811 patients were pooled, and the result indicated that smoking might promote stricture recurrence (RR=1.32, P=0.001). Based on the adjusted estimate, 11 studies with 3176 patients were pooled in the multivariate meta-analysis stage, and the result indicated that smoking might promote stricture recurrence (RR=1.35, P=0.049). There was no significant heterogeneity in both the univariate and multivariate stages.

Conclusion: Our study demonstrates that smoking may prompt stricture recurrence after the urethroplasty. Quitting smoking may be a good option for patients undergoing urethroplasty surgery.

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INTRODUCTION

When urologists deal with the urethral stricture patients by urethroplasty, one of the most worrying situations is the stricture recurrence (1). Currently, there are many definitions of stricture recurrence after urethroplasty, mainly including changes in urinary flow rate and the ability to pass 16Fr/18Fr diameter cystoscope, etc (2). However, due to the limitations of many conditions, most literature still makes the judgment based on the patient's need for further treatment. According to the literature review results, the stricture recurrence rate is about 6%-28% nowadays with different techniques or materials (3). It is important to note that once the stricture recurred, the success rate of the second operation was significantly reduced. In order to find out the possible causes of postoperative stricture recurrence, and some prognostic factors such as BMI, length of stricture, previous urethroplasty history, direct visual internal urethrotomy (DVIU) history have been reported (4). However, in addition to these risk factors that have a strong role in promoting stricture recurrence, there are still some risk factors that are relatively mild or need a long time for stricture promotion, which can only be described by a large sample size of clinical research.

Many studies have pointed out that the use of tobacco, whether it is the inhalation of cigarettes or the use of tobacco powder or e-cigarettes, will increase the level of inflammation in the body. The increase in the level of inflammation in the body is closely related to the formation and aggravation of scars, The increase in the level of inflammation in the body is closely related to the formation and exacerbation of scars, which may further increase the possibility of recurrence of stricture after urethroplasty (5). In 2010, a study pointed out tobacco consumption may lead to stricture recurrence after urethroplasty. However, in many retrospective studies, whether in univariate analysis or multivariate analysis, the role of smoking in the stricture recurrence after the urethroplasty has not been uniformly described. Some studies even mentioned that smoking could be helpful for scar healing (6). Therefore, the objective of this paper was to conduct a meta-analysis based on the reported data to obtain a regular assessment of the relationship between smoking and stricture recurrence after the urethroplasty.

It is worth noting that the statistical analysis of many retrospective studies of risk factors is usually divided into two parts, namely univariable factor regression analysis and subsequent multivariable regression analysis. Suppose only meta-analysis is performed on the results of multivariate regression analysis. In that case, it may lead to obvious selection bias (many studies only include variables that are significant in univariate regression in multivariate regression). Therefore, the results of single factor regression and multivariate regression analysis were combined separately in this study to get a more comprehensive result.

MATERIALS AND METHODS

The literature collection, data extraction, merging, and subgroup analysis methods used in this study are similar to those of our previous published studies (7).

Literature search and inclusion criteria

This meta-analysis was performed according to the principle of preferred reporting items for systematic reviews and meta-analysis (PRISMA) (8). This meta-analysis has been registered at PROSPERO (registration number: CRD42021277661). We conducted a pre-analysis to assess feasibility before entirely conducting this meta-analysis. When a preliminary literature search is carried out, and it is clear that a considerable number of high-quality, relevant studies have been published, we will conduct a follow-up detailed search and data sorting and analysis. That is why in PROSPERO registration, we truthfully mentioned that formal screening of search results against eligibility criteria and risk of bias (quality) assessment began before submission to PROSPERO. Pubmed, Embase, Web of Science, and Cochrane Library were searched to identify potential studies. The latest search date was July 1, 2022. Keywords included urethroplasty, smoking, smoker, tobacco

consumption, and stricture recurrence. Furthermore, the reference part of every candidate literature was manually screened to find possible data sources.

Detailed inclusion criteria were as follows: Patients were treated with onlay with buccal mucosa or penile fasciocutaneous flap, oral mucosa, or any other type of substitution urethroplasty anastomotic urethroplasty or any combined urethroplasty techniques for anterior or posterior urethral strictures. Odds ratio (OR), hazard ratio (HR), and relative risk (RR) with a 95% confidence interval (CI) of risk factors should be offered or could be calculated. Only English-written studies were included. Exclusion criteria: Reviews, meta-analyses, letters, comments, case serials, and conference abstracts were excluded. Studies focused on hypospadias and pediatric patients and published earlier than 2000 were excluded. Studies that did not contain regression information or enough data to be used for secondary analysis were excluded. Since few studies offered detailed smoking history information such as tobacco type (cigarettes or electronic cigarettes, etc.), smoking time, or whether current smoking, was smoking was not explicitly defined in this study. Because many studies based on adult cases did not strictly distinguish the cause of urethral stricture, this study did not exclude articles according to the cause of urethral stricture. The study was included in the analysis when the original study's smoking history variable was present. Two independent authors carried out all the title screening, abstract screening, and full-text review.

Research Quality Evaluation

All included studies were evaluated by Newcastle-Ottawa Scale (NOS) system, and two independent reviewers performed the evaluation procedure. Disagreements between the two authors should be determined by the third author (TJ)(9). According to the NOS, 7-9 score studies were considered high-level quality, 5-6 score studies were considered moderate-level, and <5 score studies were low-level quality. Low-level quality studies should not be involved in the meta-analysis.

Meta-analysis

Based on univariate and multivariate analysis results in this study, the relationship between smoking and stricture recurrence was pooled in a meta-analysis. All analysis was powered by Stata 15.0 software (Stata Corporation, College Station, TX, U.S.A.). Statistical significance was defined as $P<0.05$ in this study. Pooled estimates larger than 1 indicated that smoking would make patients more vulnerable to stricture recurrence. Heterogeneity was evaluated by I^2. When I^2 was larger than 50%, heterogeneity could be significant. If significant heterogeneity was detected, a random effect model should be applied. The primary outcomes were displayed with a forest plot. Subgroup analysis was also performed to get more detailed information. The variables included in subgroup analysis mainly include the research area, the number of participants, the recurrence rate of stricture, the type of estimates, the location of the stricture, and the type of urethroplasty surgery.

Furthermore, sensitivity analysis was performed to test the stability of meta-analysis results, and publication bias was tested by Egger's and Begg's tests. Funnel plots were used for publication-bias visual identification. After data synthesis, the final effect size should be the relative risk. This is a meta-analysis that tried to combine regression estimates. In many retrospective studies, only significant factors in the univariate logistic or Cox regression would be included in the multivariate logistic or Cox regression. Combining multivariate analysis results will undoubtedly bring selection bias if we only combine multivariate analysis results. It is necessary to perform a meta-analysis based on univariate analysis results.

The previously published preprint has detailed and described all the analysis procedures (Research Square, 10.21203/rs.2.23580/v1).

RESULT

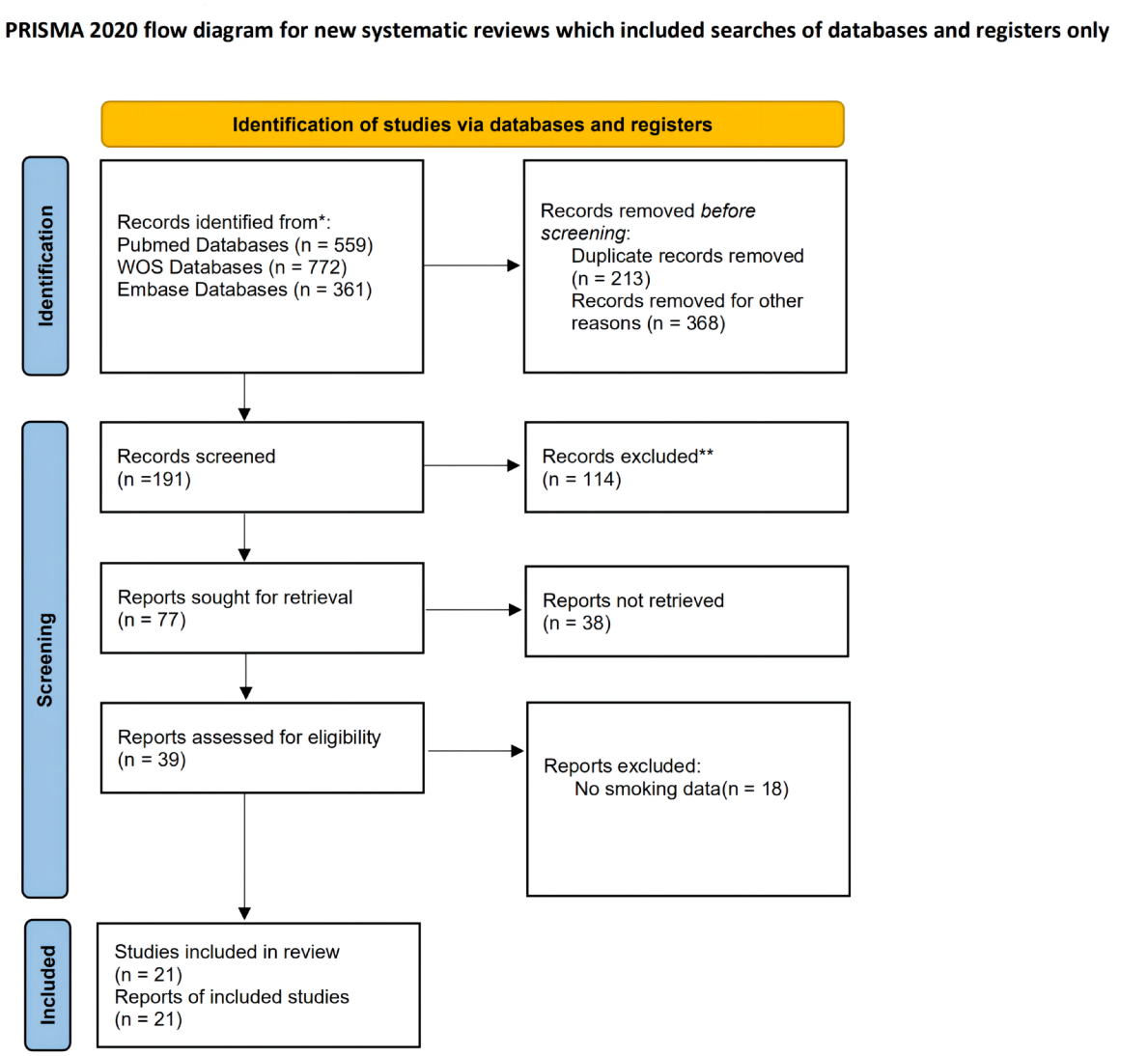
Study selection

One thousand three hundred twenty-nine studies were identified from databases in total. 14 of included studies were carried out in the North

American region, and 7 were carried out in other regions. Thirteen studies were carried out in recent 5 years, and no study earlier than 2000. Four studies focused on the anterior urethra, 5 on the bulbar urethra, 2 on the posterior urethra, and 7 studies did not limit stricture locations. Almost all studies did not define the cause of stricture. 8 of included studies used techniques for substitution urethroplasty with different materials, 3 of included studies focused on anastomotic urethroplasty.

After duplicate removal, abstract screening, and full-text reading, 21 studies were finally involved in this meta-analysis. The detailed screening procedure is displayed in Figure-1. There were 18 studies (total 5811 patients) contained smoking-stricture recurrence univariate analysis information(3, 10-26), 11 studies (total 3167 patients) contained multivariable analysis information(10, 12, 15, 16, 18-20, 27-30). Out of 20 involved studies, 19 studies are retrospective cohort studies, and only 1

Figure 1 - Study searching flow chart.



From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

For more information, visit: http://www.prisma-statement.org/

study was prospectively designed. Detailed baseline information and research quality evaluation are shown in Table-1 and Table-S1 separately.

Meta-analysis based on univariable analysis

In terms of univariate analysis, 18 studies containing 5811 patients exploring the association between smoking and stricture recurrence after urethroplasty. According to the overall meta-analysis result, smoking can make patients more vulnerable to stricture recurrence (RR=1.32, 95%CI: 1.12-1.56, P=0.001) with no significant heterogeneity found (I^2=0.0%, p=0.792) (Figure-2A). No significant publication bias was found according to Egger's test (P=0.058) and Begg's test (P=0.112) and was shown in the funnel plot (Figure-2B). Sensitivity analysis showed that the results were not significantly changed by omitting included studies one by one (Figure-2C). Further subgroup analysis results were displayed in Table 2. We found that only when strictures were located in the anterior urethra smoking could significantly negatively affect stricture recurrence (RR=1.42, 95%CI:1.03-1.96, P=0.033).

Meta-analysis based on multivariate analysis

Based on multivariate analysis, the association between smoking and stricture recurrence after urethroplasty was explored in 11 studies containing 3167 patients. According to the overall meta-analysis result, smoking can make patients more vulnerable to stricture recurrence (RR=1.35, 95%CI: 1.002-1.81, P=0.049) with no significant heterogeneity found (I^2=37.4%, p=0.09) (Figure--2A). No significant publication bias was found according to Egger's test (P=0.087) and Begg's test (P=0.062) and was shown in the funnel plot (Figure-2B). Sensitivity analysis indicated that this data synthesis might not be exactly stable (Figure-2C). Further subgroup analysis results were displayed in Table-2. Interestingly, smoking was no longer significant after anterior urethra stricture treatment (RR=2.45, 95%CI:0.70-8.66, P=0.163) but significant after posterior urethra treatment (RR=2.26, 95%CI:1.13-4.52, P=0.021) when the data were pooled using the results of the multivariable regression.

DISCUSSION

Urethral stricture is a kind of pathological stricture of the urethra, which can limit fluid transportation. Since the male urethra is significantly longer than the female urethra, and the posterior urethra is hidden in the pelvis, the urethral stricture can always bring many troubles to patients and urologists. Urethral stricture is a common urinary disease for males. There are 229-627 cases in every 100000 people, and in some susceptible groups, such as elderly men, the prevalence rate is as high as 0.6% (31). As one of the main methods to treat urethral stricture, there are many ways to implement urethroplasty, including primary anastomosis and substitution implantation. However, although many different surgical methods have been developed for different stricture degrees, lengths and locations, the success rate is still only 72% - 94%. Therefore, it is very important to find out the risk factors of recurrence of urethral stricture after urethroplasty and to prevent them. Some risk factors such as the length of stricture and etiology have attracted the attention of urologists, but other factors such as tobacco consumption have not been evaluated carefully

This meta-analysis revealed that tobacco consumption could increase the chance of stricture recurrence based on univariate and multivariate analyses. In the multivariate analysis stage, the sensitivity analysis result was not exactly stable, indicating that more multivariate analysis studies and adjusted estimates between smoking and stricture recurrence were required. In the univariate subgroup analysis, we found that anterior urethral stricture is most likely to be affected by smoking, increasing the risk of recurrence of the stricture. Similarly, patients who use substitution urethroplasty are more likely to be affected by smoking. However, similar effects were not found in the subgroup analysis based on the results of multivariable regression. This may be since fewer original studies provide the results of multivariate regression analysis. It was worth noting that in the subgroup analysis, we found that the pooled results based on HR always showed statistical significance, which may mean that the influence of smoking on the recurrence might have time-dependent distribution (For example, it was

Table 1. Characteristics of studies included in the meta-analysis.

Author	Year	Country	Stricture location	Study design	Techniques applied	Median/ Mean follow (months)	Sample size	Recurrence number	Mean or median age (year)	Definition of stricture recurrence	NOS score
Verla, et al. (25)	**2020**	**Belgium**	Anterior urethral stricture	**PCS**	Anastomotic urethroplasty/ Buccal mucosa graft/ Fasciocutaneous flap/combined technique	**62**	**474**	**81**	**NR**	**symptoms or an obstructive voiding curve on urofowmetry (<15 mL/s)**	**7**
Kinnaird, et al. (27)	2014	Canada	Anterior/posterior urethral stricture	RCS	NR	52	604	56	44.5	Cystoscopic evaluation	5
Breyer, et al. (12)	2009	USA	Anterior/posterior urethral stricture/ combined stricture	RCS	Anastomotic urethroplasty/ Buccal mucosa graft/ Fasciocutaneous flap/ combined techniques	70	381	60	41.5	peak urinary flow less than 15 cc per second and/or the radiographic evidence of stricture and further need for urethral instrumentation	8
Viers, et al. (13)	2017	USA	bulbar urethral stricture	RCS	Excision + primary anastomosis/ Substitution	64	514	74	49	the need for recurrent urethral interventions such as endoscopic treatment, subsequent catheterization or repeat urethroplasty	5
Christopher G. Keith (16)	2019	USA	bulbomembranous urethra	RCS	Primary anastomosis	30.7	116	22	72.3	Recurrence was defined by recurrent stricture ≤ 16F in caliber on cystoscopy, stricture on VCUG, and/ or operative intervention for urethral stricture disease	7

Chapman, et al. (17)	2017	Canada	bulbar stricture	RCS	BMG Onlay/ Flap Onlay/ Augmented Anastomosis/ Anastomotic/ Combined Tissue plasty	65.4	596	40	44.3	cystoscopic evaluation (inability to easily pass a 16Fr cystoscope)	7
Whitson, et al. (18)	2007	USA	Anterior Urethral Stricture	RCS	fasciocutaneous flap urethroplasty	87.6	124	26	48	Subjective and objective improvement in urinary flow, absence of radiographic evidence of stricture, and no further need for urethral instrumentation.	5
Liu, et al. (30)	2015	USA	Fossa navicularis/ Penile/ Bulbo-membranous/ Panurethral strictures	RCS	Dorsal onlay/ Ventral onlay/ Staged urethroplasty	59.3	239	66	42.9	A stricture <16F in caliber was visually present in the reconstructed segment of urethra on cystoscopy	8
Han, et al. (19)	2015	USA	Posterior urethral stricture	RCS	Excision/primary anastomosis/ Dorsal onlay (including aug-mented anasto-motic)/ Ventral onlay/ Staged/ Combined/flap/ miscellaneous	62	237	60	42.9	patient-reported recurrent urinary symptoms and urethral caliber less than 18-Fr on cystoscopy, and/or need for any subsequent intervention (including dilation, endoscopic urethrotomy or repeat urethroplasty)	5
Kahokehr, et al. (11)	2018	USA	bulbar urethral stricture	RCS	Excision + primary anastomosis/ Augmented anastomotic repair/ Onlay	28	395	23	43.41	Stricture recurrence was defined as the need for further intervention in the postoperative period as diagnosed with cystoscopy and/or RUG	5
Levy, et al. (29)	2017	USA	Bulbar/ Meatus/ Fossa/ Mem-branous/ Penile stricture	RCS	Excision + primary anastomosis/ BMG dorsal onlay	21.6	322	22	44.2	the freedom from additional procedures after urethroplasty	5
Mathur, et al. (24)	2014	India	Anterior (penile+ bulbar)/ Posterior (membranous/ bulbomembra-nous)/ Panurethra strictures	RCS + prospective data	single-stage penile preputial flap urethroplasty	42	58	11	42.2	Patient reported symptoms and retrograde urethrography	5

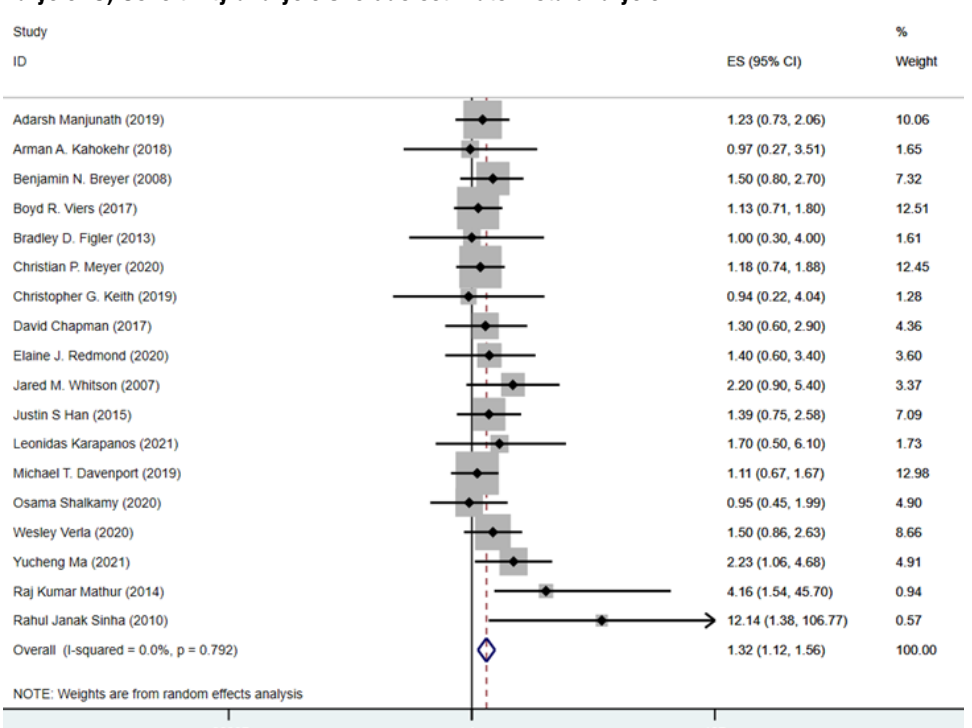
Sinha, et al. (23)	2010	India	Penile/Bulbar/ Bulbopenile/ Pananterior stricture	NRPCS	Oral mucosa graft Urethroplasty	18.2	42	11	40.2	failure was defined as the need to carry out any intervention or invasive procedure in the urethra following the complaint of decreased urinary flow by the patient	5
Manjunath, et al. (10)	2019	USA	Fossa navicularis/ Penile urethra/ Bulbar urethra/ Membranous urethra stricture	RCS	Excision and primary Anastomosis, substitution urethroplasty performed utilizing buccal mucosa, tunica vaginalis, or abdominal wall skin grafts	52.5	398	78	42.8	patient-reported recurrent urinary symptoms and urethral caliber less than 16-Fr on cystoscopy, and/or need for any subsequent intervention (including dilation, endoscopic urethrotomy, or repeat urethroplasty)	7
Figler, et al. (14)	2013	USA	Bulbar urethra stricture	RCS	Urethroplasties With Buccal Mucosa Graft	35.7	103	19	40.8	the need for endoscopic or open revision of the reconstruction or the placement of a suprapubic catheter for urinary retention	5
Meyer, et al. (15)	2020	Germany	Anterior urethra stricture	RCS	One-stage Buccal Mucosal Graft Urethroplasty	32	517	76	53.7	need for any intervention	5
Redmond, et al. (3)	2020	Canada	Bulbar Urethral Strictures	RCS	Dorsal onlay repair, anastomotic urethroplasty with dorsal BMG	78.9	507	31	45.4	Inability to easily pass a 16Fr flexible cystoscope.	7
Karapanos, et al. (20)	2021	Germany	Anterior urethra stricture	RCS	tissue-engineered oral mucosa graft urethroplasty	7	77	24	60	the need for any further treatment for recurrent stricture or a Qmax <15 mL/s	5
Davenport, et al. (21)	2019	USA	Bulbar urethral strictures	RCS	Excision and primary anastomosis	52.4	853	85	53.1	Functional emptying and lack of need for further endoscopic or open re-operative management	5

Shalkamy, et al. (22)	2020	Egypt	Anterior urethral stricture	RCS	BMG urethroplasty	49.77	266	34	37.71	The need for further intervention, including urethral dilation, was considered stricture recurrence.	5
Ma, et al. (29)	2021	China	Posterior urethra stricture	RCS	Excision and primary anastomosis	49	153	31	45	Patients received further surgical intervention or instrumentation, such as urethra dilation, urethrotomy, or any endoscopic management, patients who had any medical record about postoperative endoscopy confirmed urethral stricture, patients reported failure.	5

RCS = Retrospective Cohort Study; **NRPCS** =Non-Randomized Prospective Cohort Study; **NR** = Not Reported; **NOS** = Newcastle-Ottawa Scale; **BMG** = buccal mucosa graft.

Figure 2 – A) Forest plot of crude estimate meta-analysis between smoking and stricture recurrence. B) Funnel plot of crude estimate meta-analysis. C) Sensitivity analysis of crude estimate meta-analysis.

A



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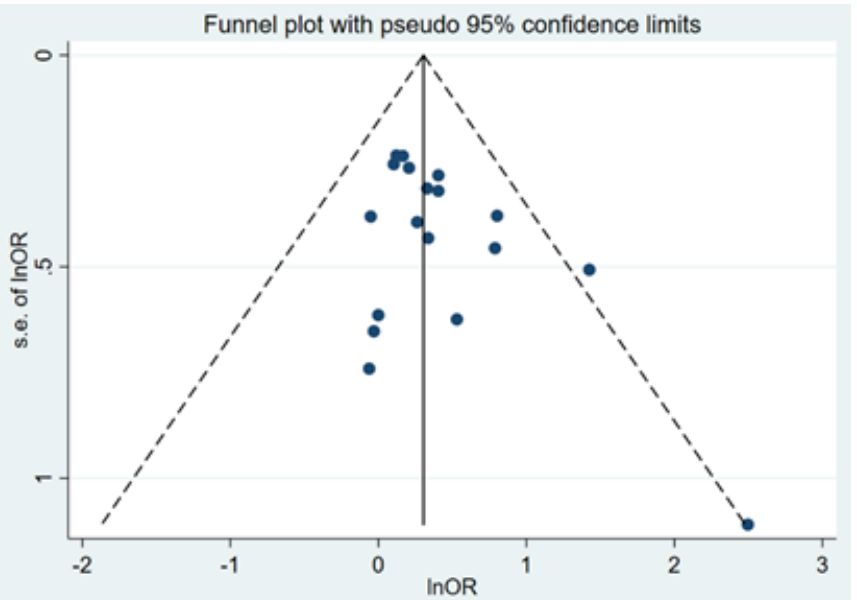
Funnel plot with pseudo 95% confidence limits
s.e. of lnOR
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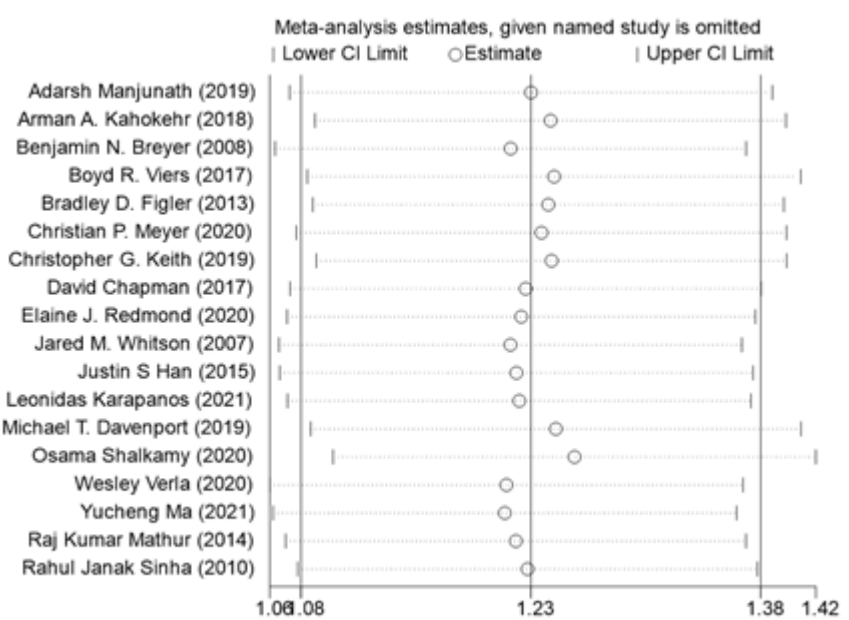
Meta-analysis estimates, given named study is omitted
Lower CI Limit
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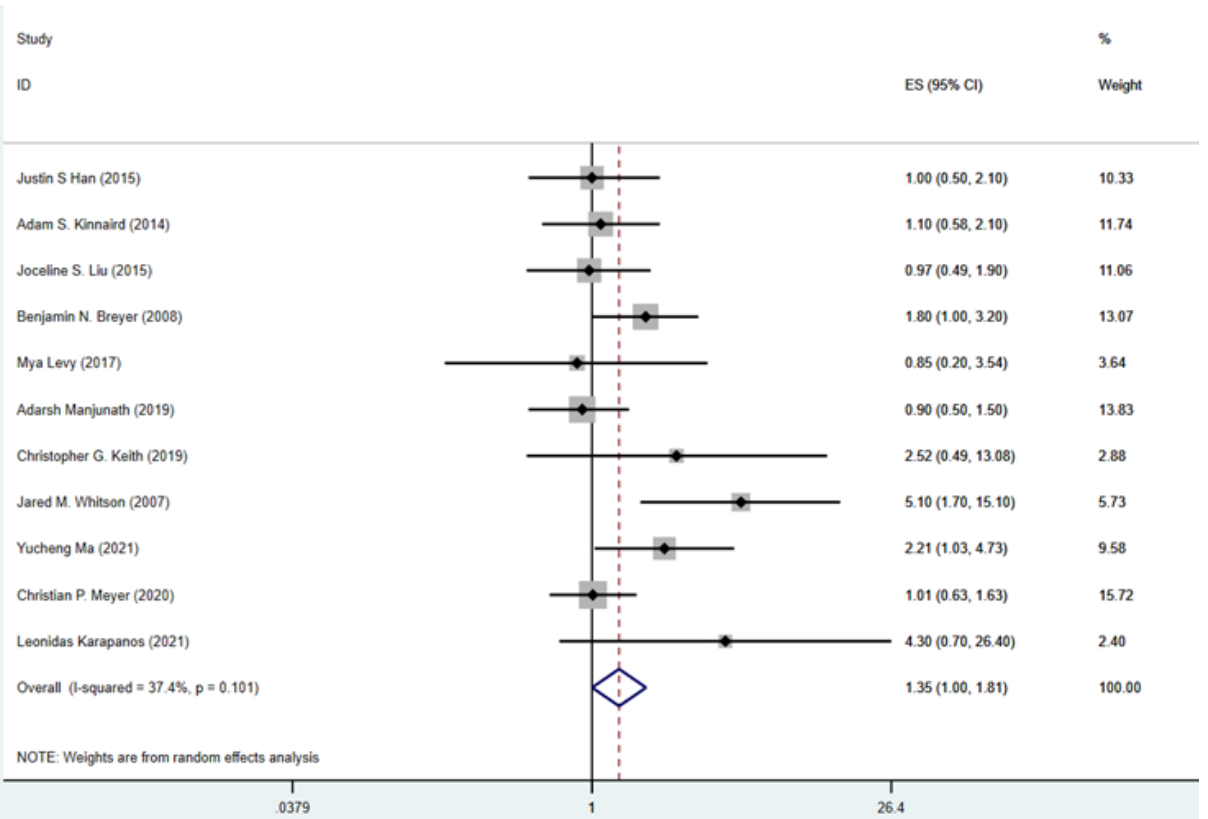
Arman A. Kahokehr (2018)
Benjamin N. Breyer (2008)
Boyd R. Viers (2017)
Bradley D. Figler (2013)
Christian P. Meyer (2020)
Christopher G. Keith (2019)
David Chapman (2017)
Elaine J. Redmond (2020)
Jared M. Whitson (2007)
Justin S Han (2015)
Leonidas Karapanos (2021)
Michael T. Davenport (2019)
Osama Shalkamy (2020)
Wesley Verla (2020)
Yucheng Ma (2021)
Raj Kumar Mathur (2014)
Rahul Janak Sinha (2010)
1.06
1.08
1.23
1.38
1.42

Table 2 - Subgroup analyses of meta-analysis.

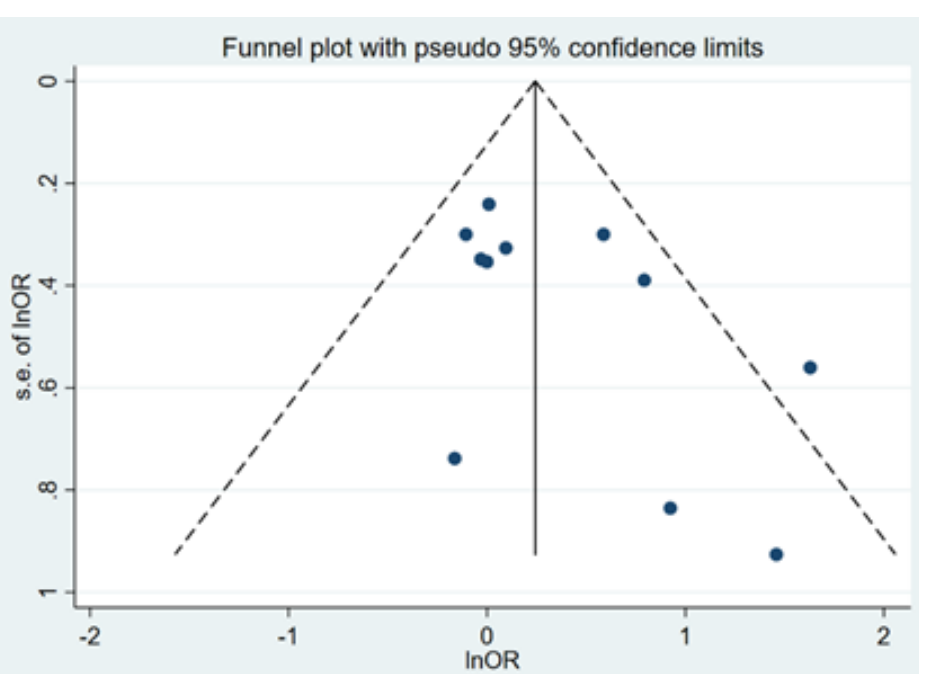
Pooled results based on univariable analysis					Pooled results based on multivariable analysis			
	Pooled estimate for stricture recurrence		Heterogeneity		Pooled estimate for stricture recurrence		Heterogeneity	
Subgroup	OR (95%CI)	P value	I2	P value	OR (95%CI)	P value	I2	P value
Region								
North American	1.26 (1.03, 1.54)	0.026	0.0%	0.983	1.29 (0.91, 1.84)	0.154	38.0%	0.126
Other	1.55 (1.07, 2.24)	0.020	29.5%	0.203	1.64 (0.78, 3.44)	0.192	56.5%	0.100
Patient number								
>300	1.24 (1.02, 1.50)	0.028	0.0%	0.993	1.12 (0.86, 1.47)	0.400	0.0%	0.479
≤ 300	1.61 (1.14, 2.28)	0.007	10.4%	0.349	1.84 (1.04, 3.26)	0.036	51.0%	0.070
Recurrence rate								
>10%	1.37 (1.14, 1.65)	0.001	0.0%	0.596	1.44 (1.01, 2.05)	0.042	48.1%	0.052
≤10%	1.18 (0.83, 1.66)	0.359	0.0%	0.947	1.05 (0.59, 1.90)	0.862	0.0%	0.748
Effect type								
HR	1.33 (1.10, 1.61)	0.004	0.0%	0.875	1.61 (1.02, 2.56)	0.043	59.2%	0.031
OR	1.37 (0.94, 1.99)	0.102	13.0%	0.330	1.08 (0.74, 1.56)	0.702	0.0%	0.649
Stricture Location								
Anterior	1.42 (1.03, 1.96)	0.033	0.0%	0.650	2.45 (0.70, 8.66)	0.163	76.9%	0.013
Bulbar	1.16 (0.83, 1.63)	0.375	0.0%	0.981	/	/	/	/
Posterior	1.83 (0.90, 3.73)	0.094	6.9%	0.300	2.26 (1.13, 4.52)	0.021	0.0%	0.887
Not specified	1.32 (1.00, 1.76)	0.054	16.7%	0.303	1.12 (0.85, 1.47)	0.428	0.0%	0.612
Urethroplasty type								
Substitution	1.44 (1.01, 2.05)	0.046	15.2%	0.310	1.70 (0.80, 3.65)	0.170	68.3%	0.024
Without substitution	1.36 (0.84, 2.22)	0.216	25.3%	0.262	2.26 (1.13, 4.51)	0.021	0.0%	0.887
Not specified	1.30 (1.03, 1.63)	0.025	0.0%	0.981	1.15 (0.85, 1.55)	0.365	0.0%	0.497
Recurrence definition								
Multiple definitions	1.47 (1.14, 1.89)	0.003	0.0%	0.685	1.81 (1.00, 3.27)	0.051	58.4%	0.035
Single definition	1.23 (0.99, 1.53)	0.066	0.0%	0.719	1.18 (0.86, 1.61)	0.311	0.0%	0.398

Figure 3 – A) Forest plot of adjusted estimate meta-analysis between smoking and stricture recurrence. B) Funnel plot of adjusted estimate meta-analysis. C) Sensitivity analysis of adjusted estimate meta-analysis.

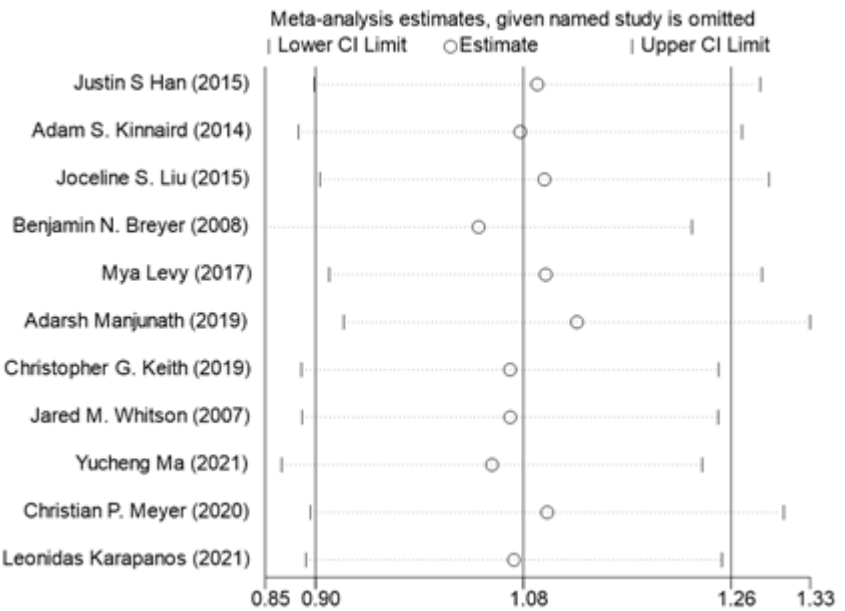
A



B



C



easier to follow the law for a long time after surgery). However, since the primary studies did not provide a KM curve, we could not perform further analysis.

Many studies have pointed out that smoking has a negative effect on healing wounds that cannot be ignored. Smoking temporarily reduces tissue oxygenation and aerobic metabolism. The inflammatory healing response is weakened by reducing inflammatory cell chemotaxis, migration function, and oxidative sterilization mechanism. In addition, the release of proteolytic enzymes and inhibitors would be unbalanced when the tissue was hypoxic or inflammatory substances were present. In addition to down-regulating collagen synthesis and deposition, reduced fibroblast migration and proliferation can also impair the proliferative response. A wound that delays healing would inevitably lead to repeated chronic local inflammation and tissue remodeling, which may be an important reason for stricture recurrence.

Furthermore, for patients who receive oral mucosa graft Urethroplasty (OMGU), a smoking history will make the general state of oral mucosa worse, leading to poor graft survival after OMGU operation and ultimately leading to an increase in stricture recurrence rate. In urethroplasty using oral mucosa as a substitution, the effect of tobacco on the oral mucosa must also be considered. Although, in some studies, patients have been advised to avoid smoking before taking oral mucosal materials, long-term smoking history can hardly avoid the impact on the viability of oral mucosa, which may further increase the impact of smoking on oral mucosa and the recurrence of stricture.

In some current urological guidelines, the effect of smoking on the stricture recurrence after urethroplasty is not mentioned. Although EAU related narratives had clearly mentioned that smoking had an important influence on the choice of surgery, in the follow-up part, it was still not mentioned that smoking is an important risk factor for postoperative recurrence.

According to the results of this meta--analysis, urologists should guide urethroplasty patients to quit smoking before and after the operation to improve the overall success rate. Some potential limitations of this study should be presented. First, although some prospective data was involved, all the included studies are retrospective. Second, although it was recognized in statistical methodology, it is still possible to bring some additional bias by combining HR and OR to get RR estimates. Third, since smoking can directly damage oral mucosa, OMGU patients with

a smoking history may have a higher recurrence ratio. It is also worth noting that the many other factors, such as postoperative complications and other factors, obviously play an important role in the recurrence of strictures, but not every primary study has fully adjusted the effects of these factors on smoking. However, in this meta-analysis, since many studies didn't offer detailed information about the OMGU technique, so OMGU subgroup analysis was not performed, further high-level evidence about smoking's effect on OMGU is needed.

CONCLUSION

Our study shows that smoking can increase stricture recurrence risk after the urethroplasty. Quitting smoking may be a good option for patients undergoing urethroplasty surgery.

ABBREVIATIONS

NOS = Newcastle-Ottawa Scale;
HR = Hazard Ratio;
OR =Odds Ratio;
RR = Relative Risk;
CI = Confidence Interval;
DVIU = Direct Visual Internal Urethrotomy;
PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-analysis;
OMGU = Oral Mucosa Graft Urethroplasty;
RCS = Retrospective Cohort Study;
NRPCS = Non-Randomized Prospective Cohort Study
B.M.G. = Buccal Mucosa Graft

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Yu-cheng Ma, Lede Lin, Zhumei Luo contributed similarly as first author.

AVAILABILITY OF DATA AND MATERIAL

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

CONFLICT OF INTEREST

None declared.

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Table S1. Newcastle-Ottawa scale score of the reviewed studies.

Study	Selection (4 stars)				Comparability (2 stars)	Outcome (3 stars)			Total score
	Representativeness score of the stricture recurrence	Selection of the stricture recurrence	Ascertainment of stricture recurrence	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts based on the design or analysis	Assessment of outcome	Was follow up long enough for outcomes to occur?	Adequacy of follow up of cohort	
Verla, et al. (25)	/	★	★	★	★	★	★	★	7
Kinnaird, et al. (27)	/	★	/	★	★	/	★	★	5
Breyer, et al. (12)	★	★	★	★	★	★	★	★	8
Viers, et al. (13)	/	★	/	★	★	/	★	★	5
Keith, et al. (16)	/	★	★	★	★	★	★	★	7
Chapman, et al. (17)	/	★	★	★	★	★	★	★	7
Whitson, et al. (18)	/	★	/	★	★	/	★	★	5
Liu, et al. (31)	★	★	★	★	★	★	★	★	8
Han, et al. (19)	/	★	/	★	★	/	★	★	5
Kahokehr, et al. (11)	/	★	/	★	★	/	★	★	5
Levy, et al. (29)	★	★	/	★	★	/	/	★	5
Mathur, et al. (24)	★	★	/	★	/	/	★	★	5
Sinha, et al. (23)	★	★	/	★	★	/	/	★	5
Manjunath, et al. (10)	/	★	★	★	★	★	★	★	7
Figler, et al. (14)	★	★	/	★	★	/	/	★	5
Meyer, et al. (15)	★	★	/	★	/	/	★	★	5
Redmond, et al. (3)	/	★	★	★	★	★	★	★	7
Karapanos, et al. (20)	/	★	/	★	★	/	★	★	5
Davenport, et al. (21)	/	★	/	★	★	/	★	★	5
Shalkamy, et al. (22)	★	★	/	★	★	/	/	★	5
Ma, et al. (29)	★	★	/	★	★	/	/	★	5

REVIEW ARTICLE

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Urological complications of COVID-19: a systematic review

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ABSTRACT

Purpose: COVID-19 continues to be an urgent World issue. Receptors of angiotensin converting enzyme 2 (ACE2), gateway of SARS-CoV-2, are present in the lungs, bladder, prostate, and testicles. Therefore, these organs face high risk of damage caused by the virus and this mechanism may explain non-respiratory symptoms of the disease.
Materials and Methods: This systematic review, guided by the PRIMSA statement, was proposed to elucidate possible urological complications of COVID-19. Searches were carried out in Medline (PubMed), Cochrane (CENTRAL), Embase, MedRxiv and LILACS. Bias analysis was made using the specific Newcastle-Ottawa Scale for each study design.
Results: Search was carried out until April 2022, and 8,477 articles were identified. Forty-nine of them were included in this systematic review. There is evidence that lower urinary tract symptoms and acute scrotum may be signs of COVID-19 in men, although in a small proportion. Also, the disease may have a transitory impact on male fertility, evidenced by several alterations in sperm counts. However, it must be clarified whether this impact is transitory, or may last for longer periods. Several patients showed reduction of total value of testosterone. Two authors linked low levels of testosterone with worse outcomes of COVID-19, suggesting that the hormone may be used as an early biomarker of the severity of the disease. Moreover, it is extremely unlikely that SARS-CoV-2 is transmitted by semen.
Conclusion: This systematic review identified possible repercussions of COVID-19 in the urinary as well as in the male reproductive system.

ARTICLE INFO

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INTRODUCTION

In December 2019 began, in the Chinese province of Wuhan, the outbreak of COVID-19 caused by a new coronavirus, the SARS-CoV-2, and on March 11th, 2020, the World Health Organization officially declared it a pandemic. Until August 2022, more than two years after the beginning of the outbreak, the virus reached all continents, affecting approximately 586 million and killed 6,4 million people (1). Although several countries have controlled the disease and have high vaccination rates, there are still some countries where immunization has not reached levels high enough to reduce virus circulation. Also, there are concerns regarding new variants and population groups that refuse the

vaccine (2-4). Therefore, elucidation of the effects of SARS-CoV-2 is still very important and relevant.

Receptors of angiotensin converting enzyme 2 (ACE2) are the gateway for the entrance of the virus into the cells. The virus uses the ACE2 receptors for entrance and serin-protease TMPRSS2 receptors for priming of spike protein, similarly to what is observed in SARS-CoV (5, 6). Besides pneumocytes type II, RNA sequencing showed that these receptors are also expressed at myocardial, esophageal, kidney proximal contorted tubules, and urothelium bladder cells (7), and at testicles (spermatogonia, Leydig and Sertoli cells) (8), cholangiocytes (9), ileum and colon enterocytes (10), suggesting that these organs are potentially damaged by SARS-CoV-2, and that this mechanism may explain non-respiratory symptoms caused by the virus. Furthermore, in 2002, during the outbreak of severe acute respiratory syndrome (SARS) it was observed that orchitis is one of the complications of SARS (11). This may be one complication of COVID-19 since SARS-CoV, and SARS-CoV-2 have 79.5% genetic similarity (12) and bind similarly to ACE2 receptors (5, 6).

Several authors have emphasized the need of urological monitoring of COVID-19 patients, not only during the disease, but also to long term complications (13-15). Therefore, a systematic review would be crucial to synthetize the major urologic aspects of SARS-CoV-2. New symptoms of the disease may be detected, expanding alert signs, helping doctors to diagnose better COVID-19, and predicting patients at risk to develop the most aggressive forms of the disease. Once the consequences to urinary and urologic systems are identified, medical decisions may be based on stronger evidence than on the ones currently used.

OBJECTIVE

The objective of this systematic review was to identify possible urological consequences or complications of patients that were infected by SARS-CoV-2.

METHODOLOGY

This systematic review was conducted according to the PRISMA statement (16), a recommendation that consists of a checklist and flow diagram to help researchers to improve the report of their systematic reviews and was registered at PROSPERO (17) under the register CRD42020206155. Systematic review of the literature was done using the database Medline (PubMed), Cochrane (CENTRAL), Embase and LILACS. The following search terms were used: (COVID-19 OR COVID19 OR Coronavirus OR 2019-nCOV OR SARS-CoV-2) AND (Urology OR Urological OR Urologic OR Urogenital OR Genitourinary OR Epididymis OR Penis OR Penile OR Prostate OR Scrotum OR Testis OR Testes OR Testicles OR Testicular OR Orchi* OR Leydig OR Sertoli OR Sperm OR Seminal OR Semen).

Two authors evaluated independently the titles and abstracts of the studies, and those meeting the inclusion criteria were selected for this review. In case of disagreements, a third author was consulted.

Articles were selected according to the following eligibility criteria: (I) COVID-19 effects on the urological system; (II) full articles, without language restrictions; (III) articles with relevant outcomes for this review.

Two authors have done the bias analysis using the Newcastle-Ottawa Scale specific to each study design.

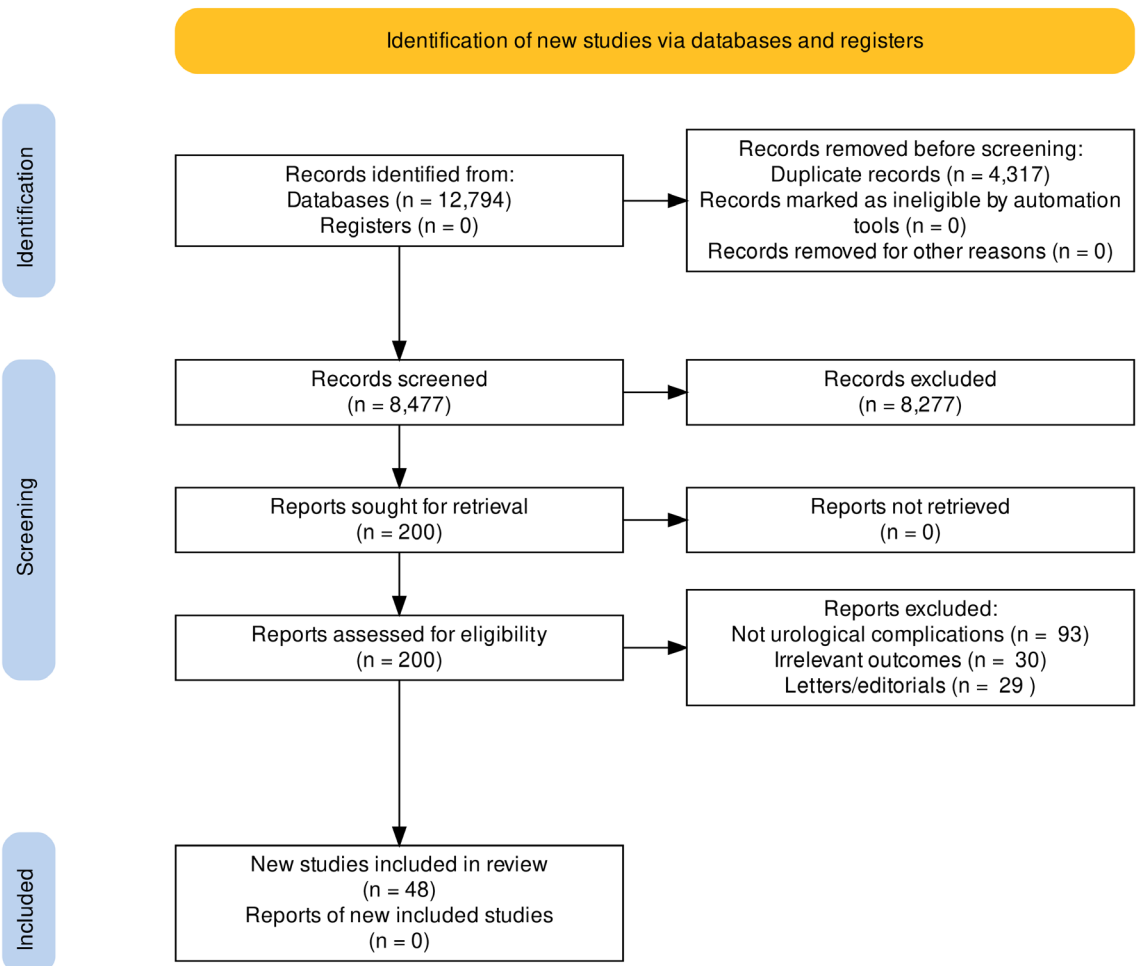
RESULTS

Search was carried out until April 2022 and retrieved a total of 12,794 articles from the scientific databases (Medline: 3,957; Embase: 4,896; LILACS: 356; CENTRAL Cochrane: 3,585). After removal of duplicates, 8,477 titles and abstracts were evaluated and 201 were selected to full reading. According to eligibility criteria, 49 articles (19-68) involving 3,008 infected patients with SARS-CoV-2 were included in this systematic review (Figure-1). Study characteristics are summarized in Table-1.

Lower urinary tract symptoms

Lower urinary tract symptoms (LUTS) were reported in 5 studies (25, 29, 40, 46, 52). Mumm et al. (52) in a series of 57 cases, reported that 7 patients showed increase of urinary frequency,

Figure 1 - Identification of new studies via databases and registers.



with a medium of 13.7 urinations at the day of admittance and 11.6 at the 5th day. Other two series, Dhar et al. (29) and Lamb et al. (46), also reported increased frequency in 39 and 4 patients, respectively. Both also verified that patients reported nocturia. Dhar et al. (29) related that 85% of patients presented 13 or more urinations per day and 87% at least 4 urinations at night. Also, Lamb et al. (46) reported urgency and urinary incontinence in 4 patients.

International Prostate Symptom Score (IPSS) was applied in 113 patients in two studies. Kaya et al. (40) did not find significant score differences among previous, during and at hospitalization due to COVID-19. This result is similar to that of Can et al. (25) in patients under 50 years of age (n=32). However, in patients with more than 50 years old (n=62) it was verified an increase of IPSS during hospitalization. Value before COVID-19 was 5.1±4.1 and during infection 9.0±6.4 (p<0. Covid 0001).

Acute scrotum

Testicle involvement was reported in some of the articles reviewed. Chen et al. (28) studying 142 patients, reported 6 with orchitis, 7 with epididymitis, 19 orchitis-epididymitis and 28 scrotal infections, being the two last more common in patients severely ill (non-severe 3 vs. severe 4; non-severe: 5 vs. severe 10, p<0.05). Ediz et al.

Table 1 - Included articles characteristics.

Study	Study design	Location	N	Age (years)	Severity	Study	Study design	Location	N	Age (years)	Severity
Achua et al. (2021) (19)	Cohort	Miami, FL, USA	6	56 (20–87)	Autopsy	La Marca et al. (2020) (43)	Case report	Modena, Italy	1	43	Death
Addar et al. (2020) (20)	Case report	Riad, Saudi Arabia	1	62	Severe	Lam et al. (2020) (44)	Case report	Pembrokeshire, United Kingdom	1	67	Death
Alkhatatbeh et al. (2020) (21)	Cohort	Zarqa, Jordan	253	43 (1–78)	Critical: 12; Severe: 48; Mild: 152; Asymptomatic: 53	Lamamri et al. (2021) (45)	Case report	Le Chesnay, France	1	62	Severe
Best et al. (2021) (22)	Cohort	Miami, FL, USA	30	40	Hospitalized: 8 Non-hospitalized: 22	Lamb et al. (2020) (46)	Cohort	Royal Oak, MI, USA	4	68 (51–85)	–
Bridwell et al. (2020) (23)	Case report	San Antonio, TX, USA	1	37	Mild	Li et al. (2020) (47)	Cohort	Beijing, China	38	–	Acute phase: 23 Recovered: 15
Burke et al. (2021) (24)	Cohort	Orlando, FL, USA	18	32 (24–57)	Moderate: 16; Mild: 2	Li H et al. (2020) (48)	Case series Cross sectional	Wuhan, China	23	40,8 ± 8,5	Ordinary: 14; Mild: 9
Can et al. (2021) (25)	Cohort	Istanbul, Turkey	94	57.5±16.6	> 3 weeks hospitalized	Ma et al. (2020) (49)	Cohort	Wuhan, China	119	39 (35–44)	Critical: 2; Severe: 14; Moderate: 100; Mild: 3
Carreño et al. (2021) (26)	Case report	Bogota, Colombia	1	39	Death	Machado et al. (2021) (50)	Cross sectional	Arkansas, USA	15	23,36 (19–43)	–
Çayan et al. (2020) (27)	Cohort	Mersin, Turkey	46	45,07 ± 18,28	ICU	Mannur et al. (2020) (51)	Case report	Telangana, India	1	36	Mild
			129		Hospital ward	Mumm et al. (2020) (52)	Case series	Munich, Germany	57	62 (59–78)	–
			46		Asymptomatic	Nie et al. (2021) (53)	Case series	Wuhan, China	5	–	–
Chen et al. (2020) (28)	Cohort	Wuhan, China	83	54,2 (38–69)	Non-Severe	Ning et al. (2020) (54)	Case series	Wuhan, China	112	55,5 (23–83)	Severe: 72; Mild: 40
			59	64 (47–78)	Severe	Pan et al. (2020) (55)	Cross sectional	Wuhan, China	34	37	–
Dhar et al. (2020) (29)	Case series	Detroit, MI, USA	39	63,5 (56 - 68,75)	–	Paoli et al. (2020) (56)	Case report	Rome, Italy	1	31	Moderate

Duarte–Neto et al. (2020) (30)	Case series	Sao Paulo, SP, Brazil	5	69 (33-83)	–	Pavone et al. (2020) (57)	Case series	Palermo, Italy	9	42 (31-60)	Mild
Ediz et al. (2020) (31)	Cohort	Istanbul, Turkey	91	38	–	Rastrelli et al. (2020) (58)	Case series	Florence, Italy	4	74,5 (59,5–85,0)	ICU/death
Erbay et al. (2020) (32)	Cohort	Karaman, Turkey	43	31.06 ± 4.2	Moderate				6	72 (33,0–83,5)	Respiratory ICU
			26	30.4 ± 4.8	Mild				21	63 (55,0–66,5)	Hospital ward
Flaifel et al. (2020) (33)	Case series	New York, NY, USA	10	49,5 (22-83)	Death	Rawlings et al. (2020) (59)	Cohort	San Diego, CA, USA	6	(28-45)	–
Fraietta et al. (2021) (34)	Case series	Sao Paulo, SP, Brazil	22	29,5 (23–33)	Mild: 20 Moderate: 2	Ruan et al. (2020) (60)	Case series	Wuhan, China	55	31,15 ± 5,32	All recovered – Severe: 32; Moderate: 31; Mild: 11
Gacci et al. (2021) (35)	Cross sectional	Florence, Italy	43	(18-65)	ICU: 5; Hospital ward: 26; non-Hospitalized: 12	Salonia et al. (2021) (61)	Case-control	Milan, Italy	34	67,0 (59,0–72,0)	Deaths
Gagliardi et al. (2020) (36)	Case report	Forte dei Marmi, Italy	1	14	Mild				51	60,0 (53,0–66,0)	Severe
Guo et al. (2020) (37)	Prospective Cohort	Jinan, China	23	41,04 ± 11,56	Moderate: 5; Mild: 18				174	57,0 (49–65,5)	Moderate
Holtmann et al. (2020) (38)	Cohort	Dusseldorf, Germany	4	40,8 ± 8,7	Moderate				27	49,0 (45,0–55,0)	Mild
			14	42,7 ± 10,4	Mild	Silverman et al. (2021) (62)	Case report	Dayton, OH, USA	1	68	Severe
Kadihasanoglu et al. (2020) (39)	Cohort	Istanbul, Turkey	12	49,9 ± 12,5	Severe	Song et al. (2020) (63)	Case series	Nanjing, China	13	(22–67)	–
			30		Moderate	Temiz et al. (2020) (64)	Cross sectional	Istanbul, Turkey	30	37,21 ± 8,59	–
			47		Mild	Xu et al. (2020) (65)	Cohort	Wuhan, China	39	60 (46,5–65,5)	Severe: 19; Moderate: 20
Kaya et al. (2020) (40)	Cohort	Eskisehir, Turkey	19	38,9 ± 13	Hospitalized	Yang et al. (2020) (66)	Case series	Wuhan, China	12	65 (42-87)	Severe: 3; Moderate: 5; Mild: 2
Kayaaslan et al. (2020) (41)	Cohort	Ankara, Turkey	16	33,5 (18–54)	Moderate: 5; Mild: 11	Zhu et al. (2020) (67)	Case report	Tianmen, China	1	30	Severe
Kim et al. (2020) (42)	Case report	Boston, MA, USA	1	42	Mild						

(31) (N=91) reported 10 patients with orchitis-epididymitis or testicular pain, and 9 with testicular edema. Pan et al. (55) (N=34) and Holtmann et al. (38) (N=18) reported respectively 6 and 1 case of testicular discomfort. Ning et al. (54) (N=112) did not report any patient with testicular edema, and Alkhatatbeh et al. (21) (N=253) did not report any patient with orchitis. Two case reports reported testicular pain (42,43), one bilateral orchitis (23) and one orchitis-epididymitis in a 14-year-old teenager (36).

La Marca et al. (43) patient presented initial bilateral testicular pain, that evolved 3 days later to dyspnea and death after one week of hospitalization. All other patients presented manifestations of acute scrotum as their initial presentation.

Autopsies

In this review, it was included 6 autopsies of patients that died due to complications of SARS--CoV-2 infection (19, 30, 33, 48, 53, 66). Yang et al. (66) reported that in 12 patients the medium of quantity of Leydig cells was inferior to control patients ($p<0.01$). In 9 patients, tubular lesion was described (4 with severe lesion, 5 moderate and 2 mild). Moreover, alterations of spermatogenesis were found in 8 patients. Nie et al. (53) performed autopsies in 5 patients, finding alterations which suggested a disfunction or reduction of Leydig cells and impaired spermatogenesis and alteration of motility of sperms. Li et al. (48) compared 6 patients with COVID-19 with 6 controls and found more apoptotic testicular cells in those infected ($p=0.018$). In addition, interstitial edema and congestion of testicles and epididymis were reported. Duarte-Neto et al. (30) described two patients with orchitis, Flaifel et al. (33) multifocal testicular microthrombus in 2 patients and Achua et al. (19) reported that 3 patients had spermatogenesis alterations.

Spermatic parameters

Several alterations such as azoospermia, oligozoospermia, criptozoospermia and teratozoospermia were found (35, 48, 51, 67). Gacci et al. (35) reported that 25.6% of patients developed some of these alterations and that concentration of sperm was lower in more severely will patients. All 9 patients (9/23) reported by Li et al. (48) with oligospermia had fathered children previously to COVID-19 through natural pregnancies. What's more, when compared to controls, sperm concentration of patients with Covid-10 were significantly lower (40.6x106/mL in controls (2, 5, 27, 61), 13.8x106/mL (2, 5, 8, 36) in patients with mild COVID-19 and 10.9x106/mL in ordinary cases). Best et al. (22) observed that patients with the disease had sperm concentrations (11.5 vs. 21.5 x 106/mL; $p=0.0048$) and total sperm count (12.5 vs. 59.2x106/ejaculation; $p=0.0024$) lower than control group. Holtmann et al. (38) observed that patients with moderate COVID-19 had reduced total sperm count (11.9 ± 13.4x106/ejaculate) and motility (total amount with progressive motility: 2.4 ± 2.7x106/mL; total amount with full motility: 4.7 ± 5.5x106) while patients with mild disease had not significant alterations (total sperm count: 243.7 ± 140.4 x 106/ejaculate; total amount with progressive motility: 125.3 ± 96.4x106; total amount with full motility: 157.1 ± 120.8x106) when compared to controls (total sperm count: 233.1 ± 234.4x106/ejaculate; total amount with full motility: 102.1 ± 102.3x106; total amount with full motility: 124.0 ± 124.9x106). Finally, Erbay et al. (32) found reduction of progressive motility ($28.81\%\pm9.7$ vs. $20.92\%\pm9.1$, $p=0.002$) and total ($48.69\%\pm12.1$ vs. $33.41\%\pm12;3$, $p<0.001$) and reduced vitality ($62\%\pm7.0$ vs. $58.1\%\pm7.1$, $p=0.03$) when compared to sperm analysis before and after the disease in patients with mild COVID-19, however without alteration of sperm concentration. In patients with moderate COVID-19 it was found reduction in all sperm parameters when compared to controls (total volume: 3.34 mL$\pm$1.1 vs. 2.74 mL$\pm$0.9, $p<0.001$; concentration: 35.01x106/mL$\pm$14.1 vs. 30.63x106/mL vs. 17.2; $p=0.008$; total count: 114.53x106±93.66 vs. 90.38x106±83.66; $p=0.001$; progressive motility: $30.16\%\pm12.1$ vs. $21.40\%\pm10.1$, $p<0.001$; total motility : $50.74\%\pm13.4$ vs. $31,42\%\pm13.3$; $p<0.001$; vitality 64.6 ± 5.6 vs. $57;4\pm6.8$, $p=0.001$).

Presence of SARS-CoV-2 in Semen

The semen of 428 patients of 19 articles was analyzed for possible presence of SARS-CoV-2 (22, 24, 34, 35, 37, 38, 41, 47-50, 54–57, 59, 60-

62). Patients included had different severity levels of COVID-19 (from asymptomatic to ICU patients) and semen samples were collected in different periods of the disease. Some patients collected at day 1 and others after 109 days of first symptoms. Of all 428 analyzed samples, only 8 presented the virus in the semen (35, 47, 50).

Priapism

Five authors reported (N=5) patients with COVID-19 and priapism (20, 26, 44, 45, 62). All had severe forms of the disease (shortness of breath and dyspnea (N=5); intubation and mechanical ventilation (N=3), oxygen support via nasal catheter (N=1), and via CPAP (N=1)) and 2 died. Also, all had a risk factor (overweight/obesity, hypertension, dyslipidemia, diabetes) and 4 were older (62-68 years old). In 5, priapism was ischemic. Interventions in 4 patients included aspiration of blood (n=2), and intracavernous administration of phenylephrine (n=2), etilephrine (n=1) or adrenaline (n=1). Of these, one died and the other three reverted priapism recovering from COVID-19. Lam's et al. (44) patient died before any treatment for priapism.

Hormones

Total Testosterone

Salonia et al. (61) reported that 89.8% of patients with COVID-19 had total testosterone lower than normal (<9.2 nmol/L) while only 14.9% in controls (2.5 (1.0-4.7) vs. 10.4 nmL/L (8.1-13.4); p<0.0001). Furthermore, lower levels of total testosterone in more severely ill patients were observed. Using multiple variated analysis made by the author, total testosterone was inversely associated with admission to ICU (OR=0.54; p<0.0001 (IC95%=0.43-0.67)) and death (OR=0.68; p=0.002 (IC95%=0.53-0.86)). Kadihasanoglu et al. (39) also showed that patients with COVID-19 presented lower values of total testosterone than controls (182.52 vs. 332 ng/dL; p<0.0001). Rastrelli et al. (58) showed in 31 patients admitted to respiratory ICU (5.0 nmol/L (1.8-7.6)) or ICU/deaths (1;0 nmol/L (0.2-1.9)) lower levels than normal (considered by the author - <8.6 nmol/L), while hospital ward patients presented normal values (medium) (8.8 (4.1-16.2)). Ma et al. (49) (COVID-19: 3.97 (3.14-5,74)) vs. control: 4.43 ng/mL (3;53-5.24); p=0.1886) and Xu et al. (65) (COVID-19: 3.3932±1.081 vs. control: 3.838 ng/mL±0.96; p<0.05) did not find significant differences among patients with COVID-19 and controls. Lastly, Çayan et al. (27) reported that patients showed a medium of normal values (308 ng/dL (18-931); normality: ≥ 300 ng/mL), but hypogonadism was observed in 113 patients (51.1%). Additionally, in 24 patients that presented the previous values of testosterone (before SARS-CoV-2 infection) a reduction of total values was observed, from 458±198 ng/dL to 315±120 ng/dL (p=0.003).

FSH

Xu et al. (65) was the only author that found significant differences of values between sick patients and health controls (although at normal range) (1.27-19.26 mLU/mL), with lower levels in patients with COVID-19 (8.763±4.952 vs. 14.407±12.918; p<0.05). Ma et al. (49) and Kadihasanoglu et al. (39) did not find differences between groups. Salonia et al. (61), showed that more severely ill patients had lower levels of FSH, although did not also find any significant differences between patients with or without COVID-19 (mild: 7.0 mU/mL (3.9-8.3); moderate: 6.9 (4.5-9.9); severe: 3.9 (2.6-5.8); deaths: 4.6 (3.8-6.4); p<0.0001). However, Çayan, et al. (27) reported that patients at ICU had higher levels than asymptomatic patients (8.41±4.38 mIU/mL vs. 5.26±2.68; p=0.02).

LH

A significant difference was found between COVID-19 patients and controls in four articles. In three of them, the patients showed higher values of LH (Ma, et al. (49)): 6.36 mIU/mL (4.63-8.37) vs. 3.38 (2.48-4.52), p<0.0001; Salonia et al. (61): 4.7 mU/mL (3.0-6.7) vs. 4.1 (3.0-5.4), p=0.005; Kadihasanoglu et al. (39): 5.67±4.52 U/L vs. 4.1±2.62, p=0.0001). On the other side, Xu et al. (65) reported that patients with COVID-19 showed lower levels than controls (5.519 mIU/mL±2.705 vs. 8.051±6.048, p<0.05). Rastrelli et al. (58) reported that patients with COVID-19 at ICU or that died presented higher levels than those admitted to hospital wards (11.2 U/L (9.0-19.3)

vs. 6.6 (4.6-9.6); p=0.037) and above normality (LH: 1.7-8.6 U/L). On the other side, Çayan et al. (27) did not find any statistically significant differences among asymptomatic patients (5.31±2.38 mIU/mL) in hospital wards (5;73±2.22) and those at ICU (5.97-3.17).

Prolactin

Kadihasanoglu et al. (39) showed that patients with COVID-19 had higher levels than controls (9.6±5.59 ug/L vs. 7.5±1.86; p=0.0007). But Xu et al. (65) did not find any difference between patients with or without COVID-19 and Çayan et al. (27) did not find significant differences among different levels of severity of the disease.

Estradiol

Xu et al. (65) reported significant differences between groups (COVID-19: 50.9±18.8 vs. controls: 34.9±18.5; p<0.05) with values above normal (≤47 pg/mL) in patients with COVID-19. Salonia et al. (61) found higher levels in patients with COVID-19 than in controls (35.0 pg/mL (22.4-44.2) vs. 23;3 (19.0-27.9); p<0.05) and, finally, Çayan et al. (27) did not find significant differences among different severities of the disease.

DISCUSSION

SARS-CoV-2 infection may cause several impacts on male urinary and genital systems. Many important changes in semen parameters in patients (azoospermia, oligozoospermia and criptozoospermia) comparing before and after infection were observed. The presence of the virus in semen was rare and reported in only 8 of the 428 samples analyzed. Patients with COVID-19 showed reduced values of total testosterone, with lower values in more critically ill patients. Furthermore, urinary frequency increase, LUTS, nocturia, urgency and incontinence were reported in several patients. Orchitis, epididymitis, edema, pain, and tenderness of testicles were also reported by several authors, demonstrating a possible testicular impact of COVID-19. Five cases of priapism were also reported. Other findings, such as IPSS alteration and changes in levels of hormones were heterogeneous.

Since the beginning of COVID-19 pandemics, there is great concern about the effects of SARS--CoV-2 on urological system, especially on the male reproductive system, due to the presence of ACE2 and TMPRSS2 receptors and the great similarity of SARS--CoV-2 and SARS-CoV. The presence of these receptors in male genital organs and in urinary bladder may explain a possible direct mechanism of action of this virus in these organs, which may explain several findings such as LUTS, IPSS increase, orchitis, epididymitis and alterations of sperm count.

Another possible explanation for the urological involvement that may occur concurrently with the direct attack of the virus is the damage caused by the inflammatory activity. COVID-19 is considered an inflammatory disease, evidenced by the cytokines storm (68). It is possible that the production of oxygen reactive species may stimulate pathways for cytokine release with exaggerated inflammatory response (69) with several cellular damage. Endothelitis caused by the virus may be one of the multiple mechanisms that cause LUTS and increase of urinary frequency (70). Duarte-Neto et al. (71) suggests that the clearance of viral antigens in the testis take longer than expected and that this can induce severe cellular changes, such as loss of Leydig cells.

In the included articles, it was observed several alterations in patients' sperm parameters, such as azoospermia, oligozoospermia and criptozoospermia. One important finding was reported by Li et al. (48), that showed that all patients with oligospermia had already fathered children by natural conception, suggesting that the disease may impair, even if transitorily, male fertility, and that the alterations may or may not be present before infection. The physiopathology of COVID-19, in particular the inflammatory response, may damage testicular cells and compromise the quality of sperm. It is also possible that fertility may be affected by several drugs used during treatment of COVID-19, such as antibiotics, corticosteroids, chloroquine, among others (72). Carneiro et al. (73) points out that there are asymptomatic epididymal injuries since they found color Doppler ultrasound changes in 42.5% of patients without symptoms of epididymitis. They hypothesize that these injuries can have deleterious impact on seminal parameters. More studies comparing spermatic parameters before and after

the disease are needed to define if infertility may be a complication of COVID-19. It is also important to follow up patients over time to verify if the impact is transitory or if it can be long-lasting.

Evidence synthesis showed that the disease may affect testosterone levels. Three articles showed that patients with COVID-19 had lower values compared to controls, particularly those more severely affected. Rastrelli et al. (58) demonstrated that the values were lower the more severe the disease. Patients with COVID-19 showed values below normal according to authors. This result is extremely important since Salonia et al. (61) univariate analysis showed that total testosterone level was inversely associated with admission to ICU, suggesting that the hormone may be an early biomarker of severity of COVID-19. Such association was also suggested by Rastrelli et al. (58). It is possible that the reduction of testosterone may last until after the recovery of COVID-19, impacting men's sex lives. Teixeira et al. (74) suggest that a decreased testosterone/luteinizing hormone ratio correlated with high levels of C-reactive protein and white blood cell count, reported by some authors, can mean a transient stage of hypogonadism. In an experimental study, Carrasco et al. (75) inoculated in rats nucleocapsid protein, that have high IgG antibodies against it in COVID-19 patients and found low serum levels of testosterone and free testosterone in these rats compared with a control group. They suggest that this hormone imbalance can be linked with a post-COVID-19 syndrome hypogonadism. However, prospective studies are needed to clarify all this hypothesis.

Regarding other hormones, the findings were heterogeneous. The great variation of findings may be due to previous diseases and conditions (before infection by SARS-CoV-2) that could have affected hormonal levels of patients. However, since these studies were observational and without previous knowledge of hormonal levels before the disease, it is not possible to conclude with accuracy the reasons of the findings.

Aside from the possible pathological effects that the disease can cause, sexual transmission of the virus was uncertain at the beginning of the pandemic. This review concluded that transmission through semen is highly unlikely. In only 8 of 428 samples analyzed the virus was found. Paoli et al. (76) suggested that virus detection could have occurred due to contamination of sample during masturbation, a non-sterile way of collecting, different from the nasal swab or venipuncture. There is also the possibility of cough contamination. Massarotti et al. (77) believes that contamination may have occurred due to residual virus from the respiratory tract. There is evidence of the presence of SARS-CoV-2 in urine (78), although in a few patients. Moreover, even if RT-PCR in semen is positive, the result only implies the presence of viral RNA in the sample, and that there may be no viable virus to be transmitted through semen ((Paoli et al. (76)). New studies are needed to determine if it is possible, even in a small proportion of patients, the transmission of SARS-CoV-2 through semen.

The COVID-19 pandemic strongly impacted all medical specialties and urology was no different. Initially, the biggest concern was about the risk of patients undergoing surgery to contract SARS-CoV-2, especially cancer patients. Anjos-Silva et al. (79) reported that the longer the hospital stay after urological surgeries, the greater the risk of contracting COVID-19 and being a fatal case. It was considered that elective urological surgeries can be safe but that urgent cases need special care to avoid contamination. Zampolli et al. (80) demonstrated that robotic and laparoscopic surgeries are safe regarding the risk of infection by SARS-CoV-2 and that the fact that they lead to a shorter hospital stay is a benefit in this situation. Several authors have been suggesting protocols to reduce the risk of infection by the virus. It is agreed that all staff members should wear Protective Personal Equipment, such as protective eyewear and N95 or PFF2 (81) masks. Furthermore, all patients should be considered suspects until proven otherwise and that all healthcare professionals should be tested in case of suspicion (82). Regarding the postponement of surgeries, especially those involving cancer patients, it is extremely important that each case is analyzed individually, considering the patient's condition and preferences and hospital conditions for big surgeries (81, 83). Cancellations and postponements of elective surgeries, medical appointments, diagnostic procedures, and non-emergency surgeries were very common in this period, strongly harming the training of residents in urology. Prezotti et al. (84)

analyzed the impact of the pandemic on urology medical residencies through questionnaires. Residents estimate that the median damage to the urological training was 6.0 [3.4 -7.7] in a scale from 0-10. In addition to the impairment in training, there was an important impact on health and quality of life, with several residents reporting weight gain, reduced physical activity, development of depressive symptoms, in addition to increased alcohol consumption and smoking. Faced with this impact on urological practice, one way to work around some of these problems is the implementation of telemedicine. Despite the impossibility of carrying out a physical examination, online consultations were of great importance in this period, reducing the chance of infection by SARS-CoV-2, promoting self--care, and enabling the training of residents (85).

Evidence of the urological involvement in patients infected by SARS-CoV-2 is limited. Bias analysis showed that only 5 articles presented low risk of bias and all others presented moderate or high risk of bias (Table-2). Most studies had low methodological quality, with only a limited number of patients, with heterogeneous characteristics regarding severity of the disease, age, comorbidities and received treatment. Lack of follow-up after COVID-19 is also another limiting factor since most studies were not longitudinal and due to the short period since the beginning of the pandemics. There are no studies that report exam results before and after the disease, limiting the extension of the conclusions of this review. It was not possible to perform a metanalysis due to impossibility to compare studies with different methodologies (study designs) and different measures used. Prospective studies with good methodologic quality, and longer follow-up are needed to determine the real impact of the disease on the male genital and urinary systems. This systematic review summarizes in a single article the main changes that COVID-19 can cause in the urological system. We describe several points that should be further investigated, such as changes in sperm parameters, since it has a potential impact on the reproductive life of men, and pathological findings of the virus attack on the testes. In the discussion, we were able to dis-

Table 2 - Bias analysis.

Author	Best et al. (2021) (22)	Burke et al. (2021) (24)	Can et al. (2021) (25)	Çayan et al. (2020) (27)	Erbay et al. (2021) (32)	Guo et al. (2021) (37)	Holtmann et al. (2020) (38)	Kadihasanoglu et al. (2021) (39)	Kaya et al. (2021) (40)	Ma et al. (2021) (49)
Selection										
1	1	1	0	1	1	1	1	1	1	1
2	1	0	0	0	1	0	1	1	0	0
3	1	1	1	1	1	1	1	1	1	1
4	0	0	1	0	1	0	0	0	0	1
Comparability										
1	1	0	0	0	1	0	1	1	0	0
Outcome										
1	1	0	1	1	1	0	1	1	1	1
2	1	0	1	0	1	1	0	0	1	1
3	1	0	1	1	1	1	1	1	1	1
Total	7	2	5	4	8	4	6	6	5	6

Cohort – Newcastle-Ottawa Scale
More information see APPENDIX 1

cuss the findings with several authors, providing urologists with an overview of the involvement of the urological system.

CONCLUSION

Although further studies are needed, this systematic review identified possible urological consequences or complications of COVID-19 such as changes of micturition pattern, urological urgencies, autopsies findings, sperm alterations, hormonal changes, and that the sexual transmission is highly unlikely.

CONFLICT OF INTEREST

None declared.

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APPENDIX 1:

Cross-sectional – Newcastle-Ottawa Scale.

Author	Achua et al. (2021) (19)	Alkhatatbeh et al. (2020) (21)	Chen et al. (2021) (28)	Ediz et al. (2021) (31)	Gacci et al. (2021) (35)	Kayaaslan et al. (2020) (41)	Lamb et al. (2020) (46)	Li et al. (2020) (47)
Selection								
1	0	1	1	1	1	1	0	0
2	1	0	0	0	0	0	0	0
3	1	1	1	1	1	1	0	1
Confounder								
1	0	0	0	0	0	0	0	0
Outcome								
1	1	1	1	0	1	1	1	1
Total	**3**	**3**	**3**	**2**	**3**	**3**	**1**	**2**
	Li et al. (2020) (48)	Machado et al. (2021) (50)	Pan et al. (2020) (55)	Rastrelli et al. (2021) (58)	Rawlings et al. (2020) (59)	Ruan et al. (2020) (61)	Temiz et al. (2021) (64)	Xu et al. (2021) (65)
Selection								
1	1	1	1	1	0	1	1	1
2	0	0	0	1	0	0	1	1
3	1	1	1	1	1	1	1	1
Confounder								
1	0	0	0	0	0	0	2	1
Outcome								
1	1	1	1	1	1	1	1	1
Total	**3**	**3**	**3**	**4**	**2**	**3**	**6**	**5**

Case report – Newcastle-Ottawa Scale.

Author	Addar et al. (2020) (21)	Bridwell et al. (2021) (23)	Carreño et al. (2021) (26)	Gagliardi et al. (2020) (36)	Kim et al. (2020) (42)	La Marca et al. (2020) (43)	Lamamri et al. (2021) (45)	Mannur et al. (2020) (51)	Paoli et al. (2020) (56)	Silverman et al. (2021) 62)	Zhu et al. (2021)(67)
Selection											
1	1	1	1	1	1	1	1	1	1	1	1
2	0	0	0	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0	0	0	0
Confounder											
1	0	0	0	0	0	0	0	0	0	0	0
Exposure											
1	1	1	1	1	1	1	1	1	1	1	1
2	0	0	0	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0	0	0	0
Total	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**	**2**

Case series – Newcastle-Ottawa Scale.

Author	Dhar et al. (2020) (29)	Flaifel et al. (2021) (33)	Fraietta et al. (2022) (34)	Li et al. (2020) (41)	Mumm et al. (2020) (52)	Nie et al. (2021) (53)	Ning et al. (2020) (54)	Pavone et al. (2020) (57)	Song et al. (2020) (63)	Yang et al. (2020) (66)
Selection										
1	1	1	1	1	1	1	1	1	1	1
2	0	0	0	0	0	0	1	1	0	1
3	0	0	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0	0	0
Confounder										
1	0	0	0	0	0	0	0	0	0	0
Exposure										
1	0	1	1	1	1	1	0	1	1	1
2	1	1	1	1	1	1	1	1	1	1
3	0	0	0	0	0	0	0	0	0	0
Total	**2**	**3**	**3**	**3**	**3**	**3**	**3**	**4**	**3**	**3**

Case-control – Newcastle-Ottawa Scale.

Author	Salonia et al. (2021) (61)
Selection	
1	1
2	0
3	1
4	1
Comparability	
1	1
Exposure	
1	1
2	1
3	1
Total	**7**

ORIGINAL ARTICLE

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Is colorectal mucosa a reasonable graft alternative to buccal grafts for urethroplasty?: A comparison of graft histology and stretch

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ABSTRACT

Objective: To compare the histological properties and stretch of colorectal mucosal grafts (CMG) and buccal mucosal grafts (BMG) and to evaluate the impact of age, medical comorbidity and tobacco use on these metrics.
Materials and Methods: Samples of BMGs from patients undergoing augmentation urethroplasty were sent for pathologic review. CMGs were collected from patients undergoing elective colectomy. CMGs were harvested fresh, at full thickness from normal rectum/sigmoid. Patients with inflammatory bowel disease, prior radiation, or chemotherapy were excluded.
Results: Seventy two BMGs and 53 CMGs were reviewed. While BMGs and CMGs were both histologically composed of mucosal (epithelium + lamina propria) and submucosal layers, the mucosal layer in CMG had crypts. The outer epithelial layers differed significantly in mean thickness (BMG 573µm vs. CMG 430µm, p=0.0001). Mean lamina propria thickness and submucosal layer thickness also differed significantly (BMG 135µm vs. CMG 400µm, p<0.0001; BMG 1090µm vs. CMG 808µm, p = 0.007, respectively). Mean delta stretch, as to length and width, was greater for CMG (118% x 72%) compared to BMGs (22% x 8%), both p<0.001.
Conclusion: CMGs and BMGs significantly differ histologically in layer composition, width and architecture, as well as graft stretch. Given its elastic properties, CMG may be useful in covering large surface areas, but its thin epithelium, thick lamina propria and additional muscularis mucosal layer could impact graft take and contracture.

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INTRODUCTION

The buccal mucosal graft (BMG) is the most widely used graft for urethral reconstruction (1). Unique qualities of BMG offer many advantages to the reconstructive urologist. The BMG is accustomed to a wet environment, it is hairless, easy to harvest, and the donor site is hidden with minimal procedure morbidity. It has a thick, elastin-rich epithelial layer, that makes it easy to handle, durable, resistant to infection and less likely to contract. In addition, its lamina propria is thin and

highly vascular, which has been proposed to help facilitate efficient imbibition and inosculation resulting in excellent graft 'take' (2-7). BMGs also fully integrate into the corpus spongiosum, while retaining their original histologic cell types-unlike preputial and tunica vaginalis grafts (8).

Certain patients may have specific relative or absolute contraindications to BMG use, such as: prior BMG harvest, surgery or radiotherapy for oral cancer treatment, active tobacco use or oral mucosal diseases. Poor oral health has also been shown to impact BMG histologic characteristics (9). Moreover, for many pan-urethral strictures or long obliterative strictures there may be insufficient total oral graft material for reconstruction (10). Therefore, surgeons must always consider both clinical factors and stricture characteristics before proceeding with surgery (11).

As an alternative to buccal grafts, colorectal mucosal grafts (CMGs) can be utilized and have recently been shown, in several small series, to successfully treat complex long urethral strictures (12-15). Although CMG outcome analysis is limited by follow-up length, the success rates seem to be similar with both grafts (2, 12, 13, 15, 16). At first glance, CMGs seem to have many of the same advantages as BMGs – they are both wet mucosa, hairless and acquired from a hidden donor site. CMGs are relatively easy to harvest using a trans-anal endoscopic microscopy (TEM) resectoscope but however, this require unique technical skill. TEM surgery carries up to a 30% risk of complications including: bleeding, perforation, fecal incontinence, and rectal stenosis (17). However, this risk been reported to be as low as 0% for CMG harvest in urologic surgery (15). In comparison, harvesting BMG grafts carries risks of bleeding, scar bleeding, scar contracture, difficulty with mouth opening and decreased oral sensation (15).

While both grafts have demonstrated clinical applicability, it is unknown how their physical and histologic properties compare. These characteristics are important to analyze as they may favor the 'take' of one graft over the other in urethral reconstruction. Therefore, the purpose of this study was to compare the histological properties and stretch characteristics of CMGs and BMGs. We hypothesized that CMG and BMGs would differ in cell layer thicknesses and in graft stretch.

MATERIALS AND METHODS

We conducted a prospective analysis of all patients who underwent BMG urethroplasty at our institution and consented to participate. CMGs were collected from all consenting patients who underwent elective colectomy or proctectomy. Colorectal patients with inflammatory bowel disease, prior radiation, or chemotherapy were excluded. All surgeries were performed between 2018 and October 2021. This study was approved by the institutional review board (AAAS3576).

The protocol and technique for BMG harvest has been previously described and was standardized across all patients (9). An ovoid graft measuring approximately 5 x 2 cm was measured and marked on the inner cheek. Graft size was standardized to limit variables that could confound graft stretch metrics. The buccal submucosa was infiltrated with 10 mL 1% lidocaine with epinephrine. The graft was sharply harvested from the inner cheek superficial to buccinator muscle. Grafts were defatted on the back table with intent to have a macroscopic whitish appearance, consistent with Group 2 dissections described by Cavalcanti et al. (18). This dissection optimizes the balance between subepithelial connective tissue preservation and adipose and muscle tissue removal (18).

Graft measurements were taken with the graft on a silicone block, both on and off stretch. Excess BMG not needed for urethral reconstruction was sent to pathology for analysis. The defect in the mouth after graft harvest was measured and recorded.

Colectomy/proctectomy was performed by a board-certified colorectal surgeon and immediately sent to pathology. All CMG specimens were obtained within six hours from resection and not contaminated by formalin. A full-thickness 5 x 2 cm was measured and marked by a member of the research team, along a segment of palpably and visibly normal colon or rectum. The graft was excised, and the mucosa was dissected off the un-

derlying muscularis propria layer. Unlike BMGs, there was no grossly visible layer that needed to be defatted. CMG dimensions were obtained in a similar fashion to BMGs, with the graft placed on a silicone block, on and off stretch.

Histological review of all grafts was performed by a single staff pathologist. Tissue was sent in 10% buffered formalin, grossed, and embedded in paraffin block. Hematoxylin and eosin (H&E) staining was performed on 5-µm tissue sections on glass slides. A minimum of 10 high power fields were examined for each prepared slide. Measurements were taken from three 100x fields using an Olympus (Japan) BX41 microscope using a U-OCM10/100 eyepiece reticle 1 mm micrometer. Digital images were taken with an Olympus QColor3 camera using QCapture software (Tokyo, Japan).

Average epithelial, lamina propria, and submucosal thickness were measured and recorded. A modified version of the previously established Oral Mucosa Rating Scale was used to quantify the type and severity of pathological mucositis for all grafts. This scale was originally developed to assess for the severity, on a scale of 0 to 3, of seven types of clinical mucosal changes considered to be manifestations of clinical oral mucositis (19).

Graft stretch was assessed using the following formula: (Ds-Dd)/(Dd)*100%. Where Ds is equal to the dimension (length or width) of the graft stretched on the silicone block after macroscopic defatting (for BMGs) or muscularis propria removal (for CMGs) and Dd is equal to the corresponding dimension (length or width) of the graft defect. Graft stretching was performed manually by using pins to secure the grafts on a block. Force required to stretch the graft over a unit of length was not measured or calculated.

Chi-squared and Fisher's exact tests were used to assess for differences in the clinical characteristics between BMG and CMG patients. Two-tailed t-tests were used to compare means and differences in graft characteristics, including stretch and histologic metrics. Individual multivariable linear regression models were used to evaluate the association between three hypothesis--driven patient-level covariates (age, tobacco use and Charlson Comorbidity Index score (CCI)), and graft characteristics for each graft type (BMG versus CMG). Statistics were performed using Stata/IC v16.1 (StataCorp LLC, College Station, Texas).

RESULTS

Seventy-two BMGs and 53 CMGs were harvested. Table-1 displays cohort characteristics. BMG patients were significantly younger than CMG patients (mean 47.8 years vs. 65.7 years, $p < 0.001$). CMG patients were more likely to have a significant history of tobacco use (22% vs. 17%, $p = 0.05$) and were generally less healthy as evidenced by the CCI (mean CCI of 3.5 vs. 1.6, $p < 0.001$). 28% of the colon specimens were ascending colon, 2% transverse, 53% sigmoid and 17% rectum. 36% underwent colectomy for diverticulitis, 51% for cancer, and 13% for other causes.

Figure-1 displays a histologic sample of a typical BMG (Figure-1A) and CMG (Figure-1B) The BMG's epithelial layer was composed of a non-keratinizing stratified squamous epithelium. A dense blood supply of capillaries, venules and lymphatics were visualized within the lamina propria (LP). The deeper submucosa layer consisted of mainly connective tissue and fat with a less densely packed blood supply. The CMG's epithelial layer on the other hand was arranged in a cryptic architecture with a simple columnar epithelium supported by a LP. The LP of the CMG also included a dense supply of venules, capillaries, and lymphatics. However, it also contained many inflammatory cells and mucin-secreting goblet cells. Like BMG, the CMG submucosa was composed of connective tissues with additional vasculature.

Table-2 displays the histologic and stretch metrics of each graft type. BMGs and CMGs were found to have similar overall graft thickness (1798µm vs. 1667µm, $p = 0.27$). However, BMGs were found to have a significantly thicker epithelium (EP), 573µm vs. 430µm ($p = 0.0001$), a thinner lamina propria (LP), 135µm vs. 400µm, ($p < 0.0001$), and a thicker submucosal layer, 1090µm vs. 808µm ($p=0.007$). A muscularis mucosa layer with a mean thickness of 44µm was present only in CMGs. CMGs were found to have a significantly greater stretch ability by length (delta stretch

Table 1 - Cohort Characteristics.

	Colorectal grafts	Buccal graft	P-value
Cohort size, n	53	72	
Age, mean (SD); [median]	65.7 (14.8); [69]	47.8 (17.1); [44]	p < 0.001
Tobacco use history, n (%)	22 (42)	17 (24)	p = 0.05
Current, n (%)	22 (42)	5 (7)	
Former, n (%)	0 (0)	12 (17)	p < 0.001
Never, n (%)	31 (58)	51 (71)	
Unknown, n (%)	0 (0)	4 (5)	
Prior Chemotherapy, n (%)	2 (4)	1 (1)	p = 0.39
Age-Adjusted CCI, mean (SD); [median]	3.5 (2.1); [4]	1.6 (2.3); [0]	p < 0.001
Age-Adjusted CCI ≤ 3, n (%)	26 (49)	59 (82)	p < 0.001
Hypertension, n (%)	29 (55)	28 (39)	p = 0.08
Diabetes, n (%)	12 (23)	7 (9)	p = 0.05
Colorectal Graft Location, n (%)		-	-
Ascending/Transverse/Descending	16 (30)	-	-
Sigmoid	28 (53)	-	-
Rectum	9 (17)	-	-

118% vs. 22%, p <0.0001) and by width (delta stretch 72% vs. 8%, p <0.0001).

Table-3 displays the results of individual multivariable linear regression models that evaluated the associations between the covariates of age, tobacco use, and CCI with graft characteristics for each graft type. Age, tobacco use, and CCI were not significantly associated with delta stretch (lengthwise or width wise) of both CMGs and BMGs (all p values > 0.05). However, increasing age was inversely correlated with epithelial thickness of BMGs (p = 0.003). This relationship was not evident with CMGs. Although tobacco use had no associated correlation with epithelial thickness of either graft type, we found a significant positive correlation between tobacco use (either former or current) and LP thickness (p = 0.035) in CMGs. We did not identify any associations between the three covariates and the submucosal thickness of either graft type.

DISCUSSION

To our knowledge, this is the first report in the literature to investigate and compare the histological and stretch characteristics of buccal and colorectal grafts. We found that each graft type had differing characteristics that could either be potentially beneficial or detrimental to graft success. We believe that our findings are important for clinical practice as they demonstrate that colorectal mucosa may not be a perfect substitute for buccal mucosa, and that this may require consideration during surgical decision making and planning.

We found that BMGs and CMGs had similar overall thicknesses but differed significantly in the dimensions of their individual cell layers. BMGs had a significantly thicker epithelium than CMGs but a significantly thinner LP. This is similar to what has been previously reported in comparisons of oral mucosa to bladder mucosa and penile

Figure 1 - Images of buccal mucosal graft histology (A) and colonic mucosal graft histology (B).

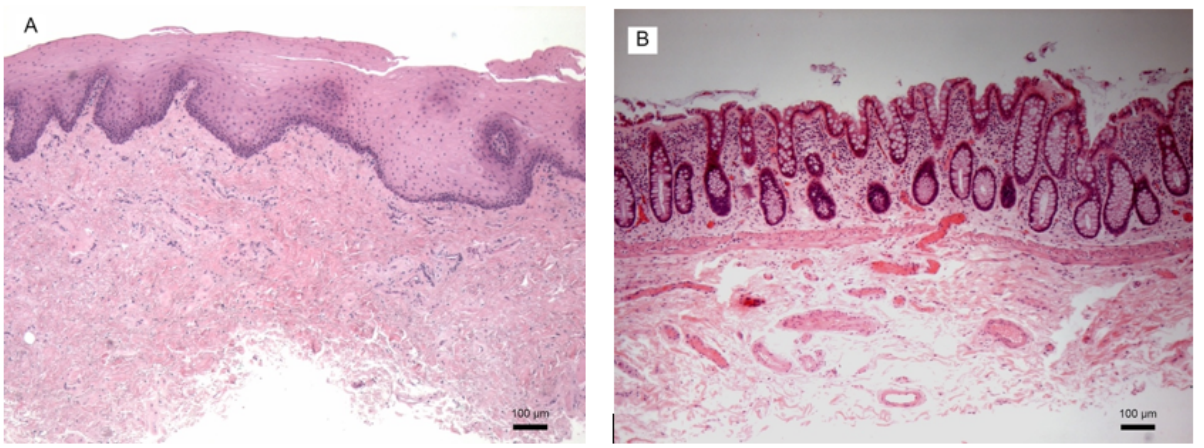

Table 2 - Graft Metrics.

	Colorectal grafts	Buccal grafts	P-value
Histologic Layers, mean (SD); [median]			
Total graft thickness (microns)	1667 (583); [1550]	1797 (689); [1780]	p = 0.27
Epithelial thickness (microns)	430 (110); [420]	573 (232); [535]	p = 0.0001
Lamina propria thickness (microns)	400 (99); [390]	135 (80); [120]	p < 0.0001
Muscularis mucosa thickness (microns)	44 (21); [40]	0 (0); [0]	p < 0.0001
Submucosal thickness (microns)	808 (486); [655]	1090 (611); [1115]	p = 0.007
Mucositis score	0 (0); [0]	0.8 (1.5); [1]	p = 0.0001
Size and Stretch Characteristics, mean SD; [median]			
Length of excision site (cm)	5.7 (1.0); [5.5]	4.7 (1.0); [4.7]	p < 0.0001
Width of excision site (cm)	2.3 (0.4); 2.1]	2.0 (0.4); [2]	p = 0.002
Length of tissue sample (cm)	10.4 (3.5); [9.5]	4.8 (1.1); [4.75]	p < 0.0001
Width of tissue sample (cm)	2.8 (0.8); [2.8]	1.7 (0.3); [1.7]	p < 0.0001
Length of tissue sample on stretch (cm)	12.2 (3.4); [11.5]	5.7 (1.3); [5.55]	p < 0.0001
Width of tissue sample on stretch (cm)	3.8 (1.0); [3.5]	2.2 (0.5); [2]	p < 0.0001
Delta Stretch Lengthwise, (% change)	118% (57); [114%]	22% (20); [20%]	p < 0.0001
Delta Stretch Widthwise, (% change)	72% (49); [59%]	8% (24); [0%]	p < 0.0001

skin (20). It is also what has driven urologists to favor oral mucosal grafts over these historic alternatives, as the dimensions of these layers are likely relevant to graft take.

Buccal mucosa is a successful substitution tissue in urethral surgery because of its inherently thick elastin-rich epithelium, which makes it tough yet easy to handle, and its thin, highly vascularized LP, or subepithelial connective tissue layer, which is believed to facilitate early inosculation and imbibition (5, 21). Its high resistance and resilience to recurrent compression, stretching

Table 3 - Results of Individual Multivariable Linear Regression Models to Evaluate Associations between Patient Level Covariates and Graft Characteristics.

	Colorectal Grafts		Buccal Grafts	
	Coeff	P-value	Coeff	P-value
Stretch Lengthwise				
Age	-0.01	0.28	0.002	0.51
Tobacco	-0.12	0.50	-0.04	0.45
CCI	0.002	0.97	0.01	0.55
Stretch Widthwise				
Age	-0.003	0.66	0.004	0.22
Tobacco	-0.06	0.73	-0.04	0.60
CCI	0.04	0.45	-0.02	0.38
Epithelial Thickness				
Age	-0.63	0.69	-8.17	0.003*
Tobacco	57.93	0.10	-23.62	0.71
CCI	9.08	0.45	27.54	0.17
Lamina Propria Thickness				
Age	1.46	0.30	-1.49	0.15
Tobacco	65.4	0.04*	14.21	0.56
CCI	0.08	0.99	7.63	0.32
Muscularis Mucosa Thickness				
Age	0.46	0.13	-	-
Tobacco	15.16	0.02*	-	-
CCI	-5.36	0.02*	-	-
Submucosal Thickness				
Age	6.55	0.37	1.12	0.88
Tobacco	114.02	0.47	-169.00	0.334
CCI	-88.80	0.11	-71.56	0.19

* Signifies statistical significance

and shearing forces are partially explained by the lamina propria-oral epithelial interface, which is made up of connective tissue projections that increase surface area and provide resistance to overlying forces (20).

Prior literature has suggested that LP width is particularly important for graft take, as it enhances basal epithelial cell viability and facilitates neovascularization of the graft (4). The LP provides vascular support and nutrition to the overlaying cellular epithelium. It also contains immune cells from the adaptive and innate immune system (22). While grafts with LPs that are too thin may be at risk of necrosis or atrophy at the recipient site (23), ones that are too thick may have compromised neovascularization. We speculate that like bladder and penile skin grafts, the relatively thick LP of the colorectal mucosa may

be disadvantageous for graft take. However, further research is needed.

Extrapolating from studies in skin grafting, we suspect that the thickness of the elastin-rich epithelial layer in mucosal grafts could impact graft contracture. Graft contracture occurs in two stages: primary and secondary contracture. Primary contracture, which refers to the immediate contraction that occurs directly after graft harvest, is due to passive recoil of elastin fibers and is directly dependent on the thickness of the elastin-rich dermis. Whereas secondary contracture, which refers to graft contraction on the wound bed, is caused by myofibroblasts deposition and is inversely related to dermal thickness (24). While additional work is needed, we suspect that, like the thicker elastin-rich dermis in full-thickness skin grafts, the thicker elastin-rich epithelium in BMGs may increase the risk of primary contracture but may mitigate the risk of secondary contracture by providing resistance to the pull of myofibroblast deposition during healing (24, 25).

Our finding that BMGs were significantly less elastic than CMGs on the back-table silicon block seems to support our hypothesis about primary graft contracture. We found that, on average, CMGs could be stretched to more than double their initial excision size on the back-table. On average a 5x2cm CMG graft, could be stretched to cover a 10.9x3.4cm defect, while a BMG could only cover a 6.1x2.2cm defect. Though little is known about the clinical importance of ex-vivo graft stretch, the significant gains in length and width in CMGs, could mean that a relatively smaller CMG could be used to cover a much larger defect than a BMG. While this characteristic would be particularly important in patients with long urethral strictures or limited oral mucosal availability, it remains unclear if CMG elasticity is durable in-vivo or if it becomes compromised by secondary graft contracture.

We also demonstrated that CMGs have an entirely extra cell layer, the muscularis mucosa (MM), compared to BMGs. This layer is relatively thin, approximating one-tenth the thickness of the epithelial and LP layers and is located deep to the LP but above the submucosa. The inner MM layer is made of a thin layer of smooth muscle. It supports and enables the mucosa to move and fold. Below it, is the submucosa – which is a thick connective tissue layer containing vasculature, lymphatics, and nerves (26). The clinical impact of this additional layer on graft 'take' and durability remains to be determined, however, its presence between the rich vascular LP layer and submucosal connective tissue layer, could represent a disadvantage to imbibition - which relies on passive exchange of nutrients into the LP. Therefore, more work is needed to determine the impact of this layer on graft outcomes.

While age, tobacco use, and CCI did not seem to have a correlation with graft stretch for each graft type, these covariates did appear to affect cell layer thicknesses. Age was inversely related to the epithelial thickness of buccal grafts. This was consistent with findings that we previously published in a smaller cohort (9). Increasing CCI was associated with decreased MM layer thickness in CMGs, suggesting that cellular health of this layer could be impacted by a patient's medical milieu. Tobacco use, including former and active smokers, was associated with increasing LP and MM thickness in CMGs. CMGs from smokers had significantly thicker LP layers than CMG from non-smokers, which is similar to what has previously been demonstrated in studies investigating histologic characteristics of uvular mucosa in smokers with obstructive sleep apnea (27) and supported by mouse studies demonstrating an association between smoking and an accumulation of inflammatory cells in the LPs of the small and large intestines (28, 29). We did not find a similar relationship between tobacco use and histologic changes in BMGs. This is supported by recent literature by Policastro et al., demonstrating no clear or clinically significant histologic or immunohistochemical differences in buccal grafts harvested from smokers compared to non-smokers (30). However, both studies had relatively small sample sizes and therefore may have been underpowered to detect an association. Further work is needed on this topic.

This study has several limitations. First, it is a single-center, single-surgeon, single-pathologist study. Second, not all BMGs resulted in pathology review. Third, our buccal patients tended to be younger and healthier, and our colorectal

patients tended to be smokers, which could have impacted the qualities of our grafts, however we did control for these factors in our models to mitigate this risk. In addition, our cohorts were small, and the CMGs were collected from several different anatomic locations along the gastrointestinal tract. And last, graft stretch was assessed manually without accounting for applied force. In addition, this was not an outcomes study – therefore we do not have clinical outcomes data to correlate with our histologic findings.

CONCLUSIONS

Our study is the first to compare the histologic properties and stretch characteristics of buccal and colorectal mucosal grafts. It also raises the question of whether certain demographic and clinical factors should influence surgeon-decision making in selecting graft type. Though more work is needed, our findings suggest that buccal grafts may continue to be a more suitable graft for urethroplasty due to their relatively thicker epithelium and thinner LP. That said, the significant elasticity of colorectal grafts may make colorectal grafts a more suitable options in patients with longer, more complex urethral strictures, or in patients who have limited oral graft availability or oral pathology. However, the durability of this elasticity during healing remains unknown. In-vivo studies, either in animal models or humans, are needed to determine if graft selection and histologic properties affect graft take, urethroplasty outcomes and the risk of stricture recurrence.

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

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Predictors of urinary function recovery after laparoscopic and robot-assisted radical prostatectomy

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ABSTRACT

Introduction: Even in the era of laparoscopic radical prostatectomy (LRP) and robot-assisted laparoscopic radical prostatectomy (RALP), we sometimes encounter patients with severe urinary incontinence after surgery. The aim of the present study was to identify predictors of urinary continence recovery among patients with urinary incontinence immediately after surgery (UIIAS).

Materials and Methods: We identified 274 patients with clinically localized prostate cancer who underwent LRP and RALP between 2011 and 2018. UIIAS was defined as a urine loss ratio > 0.15 on the first day of urethral catheter removal. Urinary continence recovery was defined as using ≤ 1 pad/day one year after surgery. In the present study, we evaluated factors affecting urinary function recovery one year after surgery among patients with urinary incontinence immediately after LRP and RALP.

Results: UIIAS was observed in 191 out of 274 patients (69.7%). A multivariate analysis identified age (< 65 years, p = 0.015) as an independent predictor affecting immediate urinary continence. Among 191 incontinent patients, urinary continence one year after surgery improved in 153 (80.1%). A multivariate analysis identified age (< 65 years, p = 0.003) and estimated blood loss (≥ 100 mL, p = 0.044) as independent predictors affecting urinary continence recovery one year after surgery.

Conclusion: The present results suggest that younger patients and patients with higher intraoperative blood loss recover urinary continence one year after surgery even if they are incontinent immediately after surgery.

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INTRODUCTION

Prostate cancer (PCa) is one of the most prevalent cancers in men. Radical prostatectomy (RP) is a radical treatment for localized PCa; however, it is associated with complications including postoperative urinary incontinence. Laparoscopic RP (LRP) was developed 25 years ago, and robot-assisted laparoscopic RP (RALP) rapidly became the standard surgery for PCa. Even in the era of LRP and RALP, we sometimes encounter patients with severe postoperative urinary incontinence. A recent review revealed no significant differences in urinary continence between RALP and open retropubic RP 12 months after surgery (1). Ficarra

et al. reported no functional superiority among surgical methods (2). Another study revealed no significant differences in the proportion of pad--free patients among open retropubic RP, LRP, and RARP groups during a one-year follow-up after RP (3). Therefore, postoperative urinary incontinence is still a serious complication for patients who undergo LRP and RALP. Since postoperative urinary incontinence has a significant impact on quality of life (4, 5), many studies have attempted to reduce urinary incontinence by using modified surgical techniques (6, 7). Despite these attempts, the prevalence of postoperative urinary incontinence has risen, paralleling the increase in the number of surgeries performed every year (8), and thus, postoperative urinary incontinence remains an important issue.

In a recent meta-analysis, continence rates twelve months after LRP ranged between 66 and 95% (2); however, those of early urinary incontinence are markedly higher. One study reported that the likelihood of a patient requiring pads after surgery was typically 70 - 80% at 6 weeks and 50 - 60% at three months (9). Although the majority of these patients regained urinary continence (using ≤ 1 pad/day) by one year (10), the patients are anxious about when their continence will improve.

Multiple factors are involved in the recovery of urinary continence after RP, including the chronological, anatomical, and oncological conditions of patients, and the surgical techniques and modifications employed (6, 11, 12). However, to the best of our knowledge, the predictors of urinary continence recovery among patients with urinary incontinence immediately after RP have not yet been elucidated in detail. Factors that improve urinary incontinence one year after surgery among patients with urinary incontinence immediately after surgery (UIIAS) currently remain unknown. We hypothesized that not only the preoperative patient background, but also intraoperative factors, such as surgical techniques, may influence urinary continence one year after surgery. Therefore, the aim of the present study was to identify predictors of urinary continence recovery among patients with urinary incontinence immediately after LRP and RALP.

MATERIALS AND METHODS

Enrollment

After approval by the Institutional Review Board (IRB number; 20160084), we identified 442 patients with clinically localized PCa at Keio University Hospital (Tokyo, Japan) between December 2011 and May 2018. We excluded patients with urinary leakage at cystography (CG) after surgery (N = 6) and urinary retention after removal of the urethral catheter (N = 13), because we were unable to calculate their urine volume. We also excluded patients who underwent salvage radiation therapy within one year of surgery (N = 8), and those with missing data, such as the lack of a urine loss ratio (ULR) description (N = 141). Therefore, 274 patients who underwent LRP (N = 143) and RALP (N = 131) were included.

We used ULR to evaluate UIIAS. ULR is defined as the weight of urine loss in a pad divided by the daily micturition volume (13, 14). Ates et al. reported that the first day on which ULR exceeded 15% correlated with an increased risk of urinary incontinence (13). Therefore, UIIAS was defined as ULR > 0.15 on the first day of urethral catheter removal in the present study. Urinary continence recovery was defined as using ≤ 1 pad/day one year after surgery; this definition has been used in previous studies (15, 16). Nurses in the urology ward provide instructions on pelvic floor muscle training (PFMT) before surgery and initiate PFMT after the removal of the urethral catheter in our hospital.

SURGICAL TECHNIQUE

LRP and RALP were performed under general anesthesia and patient-controlled intravenous analgesia. We performed LRP in a supine position and RALP was mainly performed using the same degree of Trendelenburg tilt (25º). In the case of glaucoma and stroke, we performed RALP in a supine position to prevent increases in intraocular pressure and intracranial pressure during surgery due to the prolonged use of a steep Trendelenburg position. LRP was performed using an extraperitoneal five-port approach, and the carbon dioxide insufflation pressure was typically maintained at 10 mmHg during surgery.

RALP was conducted by the same surgical team using the da Vinci® Xi surgical system. RALP was performed using both transperitoneal and extraperitoneal approaches; however, the transperitoneal approach was more frequent as it provides a wider space to work. In the present study, 117 out of 131 patients underwent RALP with a transperitoneal approach. The remaining 14 patients underwent RALP with an extraperitoneal approach due to a history of abdominal surgery, glaucoma, and stroke. RALP was performed using six ports, and the carbon dioxide insufflation pressure was typically maintained at 10 mmHg during surgery. Pelvic lymph node dissection including the bilateral internal iliac, external iliac and obturator lymph nodes was performed in both LRP and RALP. The dorsal venous complex (DVC) was processed by cold incision and selective sutures in both LRP and RALP. In either method, hemostasis by thermal coagulation was minimized. We also performed preservation of the urethral length and posterior reconstruction of the rhabdosphincter (Rocco's stitch) before vesicourethral anastomosis in both LRP and RALP. On the other hand, we did not perform bladder neck preservation, puboprostatic ligaments sparing the preservation of the endopelvic fascia, Retzius sparing, or complete anterior preservation. Nerve sparing was conducted according to the location of the lesion and requests by patients (Supplementary Table-1). After vesicourethral anastomosis, the integrity of the anastomosis was tested by instilling 100 mL of saline into the bladder with a urethral catheter. At the end of surgery, a 5-mm drainage tube was placed in the vesicourethral anastomotic part. We estimated blood loss based on the observation of the weight of surgical gauze used and the amount of fluid in the suction device during surgery. CG was performed on the fourth postoperative day (POD), on average, and the urethral catheter was removed if there was no urinary leakage.

Statistical analysis

The relationships between clinicopathological backgrounds and urinary continence one year after surgery or first day ULR were analyzed by the chi-squared test or Mann-Whitney U test. Independent variables examined in the present study were patient age (< 65 years vs. ≥ 65 years), body mass index (BMI) (≤ 22 kg/m2 vs. > 22 kg/m2), the presence of diabetes (DM) (yes vs. no), prostate specific antigen (PSA) level (≤ 10 ng/mL vs. > 10 ng/mL), prostate volume (≤ 30 mL vs. > 30 mL), clinical T stage (≤ T2 vs. ≥ T3), Gleason score (< 7 vs. ≥ 7), surgical method (LRP vs. RALP), nerve-sparing (including unilateral or bilateral) or not (yes vs. no), estimated blood loss (EBL) (< 100 mL vs. ≥ 100 mL), the surgical time (< 200 minutes vs. ≥ 200 minutes), and the duration of urethral catheterization (until 4 POD vs. over 5 POD). Univariate and multivariate analyses that predict urinary continence one year after surgery or first day ULR were performed using logistic regression models.

All reported p values were two-sided, and significance was set at $p < 0.05$. These analyses were performed with SPSS ver. 25.0 statistical software package (IBM Corp., Armonk, NY, USA).

The Ethics Committee of the Keio University School of Medicine waived the requirement for informed consent for this study.

RESULTS

Among 274 patients, median age at the time of surgery was 67 (47 - 76) years, median BMI was 23.7 (15.2 - 37.7) kg/m2, the median PSA value was 6.9 (3.8 - 72.9) ng/mL, the median prostate volume was 30.0 (10.3 - 80.4) mL, the median volume of EBL was 150 (30 - 2250) mL, the median surgical time was 199 (70 - 459) minutes, and median first day ULR was 0.31 (0.00 - 1.00) (all values are medians (range) (Table-1).

Urinary continence one year after surgery was observed in 233 out of 274 patients (85.0%). A multivariate analysis identified age (< 65 years, $p = 0.002$) and first day ULR (≤ 0.15, $p = 0.005$) as independent predictors affecting urinary continence one year after surgery in all patients. Other clinical and pathological features were not associated with urinary continence one year after surgery (Table-2).

Among 274 patients, 83 (30.3%) were continent immediately after surgery. A multivariate analysis identified age (< 65 years, $p = 0.015$) as

Table 1 - Clinicopathological backgrounds in overall patients.

Characteristic	Total	first day ULR ≤ 0.15	first day ULR > 0.15	p value	Continence	Incontinence	p value
No. of patients	274	83	191		233	41	
Age (years)				**0.027**			**< 0.001**
Median	67	65	67		66	69	
Range	47 - 76	47 - 76	48 - 76		47 - 76	60 - 75	
BMI (kg/m²)				**0.755**			**0.494**
Median	23.7	23.4	23.8		23.6	24.0	
Range	15.2 - 37.7	15.2 - 37.7	15.8 - 33.9		15.2 - 37.7	18.3 - 30.8	
DM				**0.421**			**0.498**
Yes	24	9	15		20	4	
No	250	74	176		213	37	
PSA (ng/mL)				**0.354**			**0.387**
Median	6.9	6.3	7.0		6.8	7.5	
Range	3.8 - 72.9	4.0 - 47.9	3.8 - 72.9		4.0 - 72.9	3.8 - 27.0	
Prostate volume (mL)				**0.265**			**0.792**
Median	30.0	29.5	30.2		29.8	30.4	
Range	10.3 - 80.4	15.1 - 61.4	10.3 - 80.4		10.3 - 80.4	15.3 - 67.1	
Clinical T stage (n)				**0.752**			**0.387**
≤ T2	253	76	177		216	37	
≥ T3	21	7	14		17	4	
Gleason score (n)				**0.420**			**0.572**
< 7	33	8	25		28	5	
≥ 7	241	75	166		205	36	
Surgical method (n)				**0.218**			**0.136**
LRP	143	48	95		126	17	
RALP	131	35	96		107	24	
Nerve sparing (n)				**0.640**			**0.723**
Performed	61	17	44		51	10	
Not performed	213	66	147		182	31	
Blood loss (mL)				**0.577**			**0.208**
Median	150	125	150		151	142	
Range	0 - 2250	0 - 800	0 - 2250		0 - 2250	0 - 600	
Surgical time (minutes)				**0.472**			**0.122**
Median	199	191	200		195	210	
Range	70 - 459	91 - 314	70 - 459		70 - 459	115 - 420	
Urethral catheter removal (POD)				**0.079**			**0.166**
Median	4	4	4		4	4	
Range	2 - 9	2 - 6	2 - 9		2 - 9	2 - 6	
First day ULR							**< 0.001**
Median	0.31	-	-		0.28	0.52	
Range	0.00 - 1.00	-	-		0.00 - 1.00	0.07 - 1.00	

BMI = body mass index; DM = diabetes mellitus; LRP = laparoscopic radical prostatectomy; POD = postoperative day; PSA = prostate specific antigen; RALP = robot-assisted laparoscopic radical prostatectomy; ULR = urine loss ratio

Table 2 - Predicting of urinary continence at one year after surgery.

Characteristic	Total	Univariate					Multivariate		
		Continence		Incontinence		p value	OR	95% CI	p value
No. of patients	274	233	85.0	41	15.0				
Age						**0.001**	**4.113**	**1.646 - 10.275**	**0.002**
< 65 years	90	87	37.3	3	7.3				
≥ 65 years	184	146	62.7	38	92.7				
BMI						**0.854**			
≤ 22 kg/m²	70	60	25.8	10	24.4				
> 22 kg/m²	204	173	74.2	31	75.6				
DM						**0.807**			
Yes	24	20	8.6	4	9.8				
No	250	213	91.4	37	90.2				
PSA						**0.686**			
≤ 10 ng/mL	207	175	75.1	32	78.0				
> 10 ng/mL	67	58	24.9	9	22.0				
Prostate volume						**0.971**			
≤ 30 mL	153	130	55.8	23	56.1				
> 30 mL	121	103	44.2	18	43.9				
Clinical T stage						**0.586**			
≤ T2	253	216	92.7	37	90.2				
≥ T3	21	17	7.3	4	9.8				
Gleason score						**0.974**			
< 7	33	28	12.0	5	12.2				
≥ 7	241	205	88.0	36	87.8				
Surgical method						**0.139**			
LRP	143	126	54.1	17	41.5				
RALP	131	107	45.9	24	58.5				
Nerve sparing						**0.723**			
Performed	61	51	21.9	10	24.4				
Not performed	213	182	78.1	31	75.6				
Blood loss						**0.083**			
< 100 mL	82	65	27.9	17	41.5				
≥ 100 mL	192	168	72.1	24	58.5				
Surgical time						**0.295**			
< 200 minutes	141	123	52.8	18	43.9				
≥ 200 minutes	133	110	47.2	23	56.1				
Urethral catheter removal						**0.147**			
Until 4 POD	223	193	82.8	30	73.2				
Over 5 POD	51	40	17.2	11	26.8				
First day ULR						**0.002**	**5.710**	**1.690 - 19.292**	**0.005**
≤ 0.15	83	80	34.3	3	7.3				
> 0.15	191	153	65.7	38	92.7				

BMI = body mass index; CI = confidence interval; DM = diabetes mellitus; LRP = laparoscopic radical prostatectomy; OR = odds ratio; POD = postoperative day; PSA = prostate specific antigen; RALP = robot-assisted laparoscopic radical prostatectomy; ULR = urine loss ratio / All values are frequency (proportion).

an independent predictor affecting urinary continence immediately after surgery. Other clinical and pathological features were not associated with urinary continence immediately after surgery (Table-3).

We then evaluated the remaining 191 patients who were incontinent immediately after surgery. Among them, 153 patients (80.1%) showed improved urinary continence one year after surgery, while 38 (19.9%) remained incontinent. A multivariate analysis identified age (< 65 years, p = 0.003) and EBL (≥ 100 mL, p = 0.044) as independent predictors affecting urinary continence recovery one year after surgery. Other factors were not independent predictors of urinary continence recovery among patients with UIIAS (Table-4).

DISCUSSION

Even in the era of LRP and RALP, urinary incontinence after RP remains a distressing complication that affects postoperative quality of life (5, 7, 11, 12). The precise etiology of postoperative urinary incontinence is unclear (17, 18). However, previous studies have suggested selective suture ligation of the DVC to preserve the rhabdosphincter and underlying neurovascular components, which may improve the recovery of urinary continence (17). Other studies revealed that Retzius-sparing RALP contributed to postoperative urinary continence (19, 20). These findings indicate the importance of reducing the complications of postoperative urinary incontinence by selecting the optimal surgical procedure. While most patients with UIIAS will recover their urinary function by one year (2, 3, 9, 10), those who do not may require additional medical treatment or surgery (21). Therefore, we need to identify patients at a higher risk of postoperative urinary incontinence even one year after surgery among those with UIIAS.

The present results revealed two predictors of urinary function recovery. Age was an independent predictor of both immediate continence and the recovery of urinary continence. According to previous studies, increased age is associated with an increased prevalence of postoperative incontinence (18, 22, 23). The mechanism underlying age-related postoperative urinary incontinence currently remains unclear (17, 18). Strasser et al. noted age-dependent decreases in the density of striated muscle cells in necropsies, and concluded that this may be the main reason for the higher incidence of urinary incontinence with increasing age (24). Other studies have suggested that the natural decrease in rhabdosphincter cells with aging contributes to the increasing incidence of stress incontinence with age, and that this process may be further accelerated by the surgical trauma of RP (18). They also speculated that the healing process leading to the restitution of normal function was less successful with increasing age. Many clinical and animal studies at the cellular and molecular levels examined age-related changes and delays in wound healing (25). Age is a risk factor for impaired wound healing. Therefore, young people are unlikely to have UIIAS, and even if they do, the repair of sphincter tissue is likely to occur. This is considered to improve urinary function one year after surgery. The present results on age and urinary continence are supported by previous findings.

High EBL (≥ 100 mL) at LRP and RALP was identified as an independent predictor of urinary continence recovery. This result is considered to be related to the content of the surgical technique. In a previous study that evaluated the relationship between EBL and postoperative urinary incontinence, blood loss did not affect continence rates 24 months after surgery (26). Preisser et al. recently reported on the relationship between EBL during RP and postoperative urinary function (27). They identified 2,720 patients who underwent RALP between 2009 and 2015, and defined EBL of 150 mL or less as low, EBL exceeding 400 mL as high and 150 - 400 mL as medium. High EBL was an independent predictor for seven days of incontinence in patients undergoing RALP. However, high EBL at RALP was not an independent predictor of incontinence three months or one year after surgery (27). They considered one of the biological reasons for these findings to blood loss being a recoverable factor within the normal hematopoietic capacity. Furthermore, high EBL incre-

Table 3 - Predicting of the first day ULR ≤ 0.15.

Characteristic	Univariate					Multivariate		
	first day ULR ≤ 0.15		first day ULR > 0.15		p value	OR	95% CI	p value
No. of patients	83	30.3	191	69.7				
Age					**0.015**	**1.943**	**1.137 - 3.322**	**0.015**
< 65 years	36	43.4	54	28.3				
≥ 65 years	47	56.6	137	71.7				
BMI					**0.951**			
≤ 22 kg/m²	21	25.3	49	25.7				
> 22 kg/m²	62	74.7	142	74.3				
DM					**0.423**			
Yes	9	10.8	15	7.9				
No	74	89.2	176	92.1				
PSA					**0.315**			
≤ 10 ng/mL	66	79.5	141	73.8				
> 10 ng/mL	17	20.5	50	26.2				
Prostate volume					**0.219**			
≤ 30 mL	51	61.4	102	53.4				
> 30 mL	32	38.6	89	46.6				
Clinical T stage					**0.752**			
≤ T2	76	91.6	177	92.7				
≥ T3	7	8.4	14	7.3				
Gleason score					**0.422**			
< 7	8	9.6	25	13.1				
≥ 7	75	90.4	166	86.9				
Surgical method					**0.219**			
LRP	48	57.8	95	49.7				
RALP	35	42.2	96	50.3				
Nerve sparing					**0.641**			
Performed	17	20.5	44	23.0				
Not performed	66	79.5	147	77.0				
Blood loss					**0.535**			
< 100 mL	27	32.5	55	28.8				
≥ 100 mL	56	67.5	136	71.2				
Surgical time					**0.735**			
< 200 minutes	44	53.0	97	50.8				
≥ 200 minutes	39	47.0	94	49.2				
Urethral catheter removal					**0.409**			
Until 4 POD	70	84.3	153	80.1				
Over 5 POD	13	15.7	38	19.9				

BMI = body mass index; CI = confidence interval; DM = diabetes mellitus; LRP = laparoscopic radical prostatectomy; OR = odds ratio; POD = postoperative day; PSA = prostate specific antigen; RALP = robot-assisted laparoscopic radical prostatectomy; ULR = urine loss ratio / All values are frequency (proportion).

Table 4 - Predicting of urinary continence at one year after surgery in patients with UIIAS.

Characteristic	Total	Univariate					Multivariate		
		continence		incontinence		p value	OR	95% CI	p value
No. of patients	191	153	80.1	38	19.9				
Age						**< 0.001**	**9.479**	**2.181 - 41.196**	**0.003**
< 65 years	54	52	34.0	2	5.3				
≥ 65 years	137	101	66.0	36	94.7				
BMI						**0.756**			
≤ 22 kg/m²	49	40	26.1	9	23.7				
> 22 kg/m²	142	113	73.9	29	76.3				
DM						**0.496**			
Yes	176	142	92.8	34	89.5				
No	15	11	7.2	4	10.5				
PSA						**0.696**			
≤ 10 ng/mL	141	112	73.2	29	76.3				
> 10 ng/mL	50	41	26.8	9	23.7				
Prostate volume						**0.797**			
≤ 30 mL	102	81	52.9	21	55.3				
> 30 mL	89	72	47.1	17	44.7				
Clinical T stage						**0.403**			
≤ T2	66	54	35.3	12	31.6				
≥ T3	125	99	64.7	26	68.4				
Gleason score						**0.989**			
< 7	25	20	13.1	5	13.2				
≥ 7	166	133	86.9	33	86.8				
Surgical method						**0.295**			
LRP	95	79	51.6	16	42.1				
RALP	96	74	48.4	22	57.9				
Nerve sparing						**0.746**			
Performed	44	36	23.5	8	21.1				
Not performed	147	117	76.5	30	78.9				
Blood loss						**0.046**	**2.207**	**1.020 - 4.777**	**0.044**
< 100 mL	55	39	25.5	16	42.1				
≥ 100 mL	136	114	74.5	22	57.9				
Surgical time						**0.406**			
< 200 minutes	97	80	52.3	17	44.7				
≥ 200 minutes	94	73	47.7	21	55.3				
Urethral catheter removal						**0.271**			
Until 4 POD	153	125	81.7	28	73.7				
Over 5 POD	38	28	18.3	10	26.3				

BMI = body mass index; CI = confidence interval; DM = diabetes mellitus; LRP = laparoscopic radical prostatectomy; OR = odds ratio; POD = postoperative day; PSA = prostate specific antigen; RALP = robot-assisted laparoscopic radical prostatectomy; UIIAS = urinary incontinence immediately after surgery; ULR = urine loss ratio
All values are frequency (proportion).

Supplementary Table 1 - Preservation procedure in the present study.

Performed	Not performed	Depending on the case
urethral length preservation	bladder neck preservation	nerve sparing
selective suturing of dorsal venous complex	puboprostatic ligaments sparing preservation of the endopelvic fascia	
	complete anterior preservation	
	Retzius sparing	

ases the risk and area of coagulation hemostasis, which may be an exacerbating factor in UIIAS. Lei et al. demonstrated that the athermal procedure of DVC had a positive effect on postoperative urinary continence (17). Therefore, minimal coagulation hemostasis during surgery may lead to an increase in EBL, and this has the advantage of improving urinary continence. If the increases in EBL are not due to minimal coagulation hemostasis, but mere carelessness at surgery, urinary incontinence may not recover immediately or one year after surgery. As described in the Materials and Methods section, we use minimal coagulating hemostasis with cold incision and selective suturing to treat DVC. The results obtained revealed that first day ULR did not deteriorate even in high EBL patients. In contrast, urinary incontinence improved one year after surgery in high EBL patients, as reported by Preisser et al. (27). The results of the present study suggest that minimal coagulating hemostasis improved urinary function within one year.

We did not identify any influence of BMI or prostate volume on postoperative urinary continence. Although previous studies reported that a lower BMI and smaller prostate volume were associated with the better recovery of urinary continence (11, 12), these findings are controversial in terms of the relationship between obesity and urinary incontinence after RP (28). Another study showed that the influence of prostate volume on continence varied (29).

The present study has some limitations. This was a single institution study, and the cohort was small. Further studies with larger sample sizes are needed to confirm the predictors of urinary function recovery among patients with UIIAS. Furthermore, this study was not conducted as a single-surgeon series. Despite all surgeons using virtually the same techniques, slight differences in procedures among surgeons may have affected postoperative urinary continence. In addition, since this was a retrospective study, we were unable to analyze possible predictors, such as the preoperative urinary condition. Despite these limitations, the present study is original in that it focused on patients with UIIAS. Moreover, it is important to note that intraoperative techniques, such as minimal coagulating hemostasis and cold incision, may have contributed to improvements in urinary incontinence.

CONCLUSION

The present study revealed that a young age and higher intraoperative blood loss at LRP and RALP are predictors of urinary function recovery among patients with UIIAS. The results of the present study may help in explaining to patients with UIIAS the importance of surgical techniques, such as minimal coagulation hemostasis.

ABBREVIATIONS

LRP = laparoscopic radical prostatectomy
RALP = robot-assisted laparoscopic radical prostatectomy
UIIAS = urinary incontinence immediately after surgery
PCa = prostate cancer
RP = radical prostatectomy
CG = cystography
DVC = dorsal vein complex
POY = postoperative year
POD = postoperative day
ULR = urine loss ratio
BMI = body mass index
DM = diabetes mellitus
PSA = prostate specific antigen
EBL = estimated blood loss

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CONFLICT OF INTEREST

None declared.

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Identification and validation of a novel prognostic model based on platinum resistance-related genes in bladder cancer

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ABSTRACT

Background: The depth of response to platinum in urothelial neoplasm tissues varies greatly. Biomarkers that have practical value in prognosis stratification are increasingly needed. Our study aimed to select a set of BC (bladder cancer)-related genes involved in both platinum resistance and survival, then use these genes to establish the prognostic model.

Materials and Methods: Platinum resistance-related DEGs (differentially expressed genes) and tumorigenesis-related DEGs were identified. Ten most predictive co-DEGs were acquired followed by building a risk score model. Survival analysis and ROC (receiver operating characteristic) plot were used to evaluate the predictive accuracy. Combined with age and tumor stages, a nomogram was generated to create a graphical representation of survival rates at 1-, 3-, 5-, and 8-year in BC patients. The prognostic performance was validated in three independent BC datasets with platinum-based chemotherapy. The potential mechanism was explored by enrichment analysis.

Results: PPP2R2B, TSPAN7, ATAD3C, SYT15, SAPCD1, AKR1B1, TCHH, AKAP12, AGLN3, and IGF2 were selected for our prognostic model. Patients in high- and low--risk groups exhibited a significant survival difference with HR (hazard ratio) = 2.7 ($p < 0.0001$). The prognostic nomogram of predicting 3-year OS (overall survival) for BC patients could yield an AUC (area under the curve) of 0.819. In the external validation dataset, the risk score also has a robust predictive ability.

Conclusion: A prognostic model derived from platinum resistance-related genes was constructed, we confirmed its value in predicting platinum-based chemotherapy benefits and overall survival for BC patients. The model might assist in therapeutic decisions for bladder malignancy.

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INTRODUCTION

Bladder cancer (BC) is the 10th most common cancer in the World (https://www.wcrf.org/cancer-trends/bladder-cancer-statistics), which carries a substantial social and financial burden. There were 573,278 new bladder cancer cases and 212,536 deaths worldwide in 2020 (1). Non-muscle-invasive bladder cancer (NMIBC) accounts for approximately 75% of BC patients, muscle--invasive bladder cancer (MIBC) accounts for 25% but has highly malignant potential and is closely

related to mortality (3, 4). Platinum-based regimens have been the backbone treatment for MIBC patients in the first-line setting (5). Unfortunately, only half of patients were sensitive to these treatment (6), and a considerable proportion of patients who were initially sensitive to platinum will develop an acquired resistance during their treatment cycle, leading to a worse progression-free survival (PFS) or overall survival (OS) of patients with MIBC (7). Despite of similar clinicopathology features, the individual heterogeneity of genetics among malignancy cells brings significant differences in therapeutic response and outcomes, stressing the vital necessity for identifying platinum resistance biomarkers as well as the clinical route of BC.

Recent studies have discovered a series of biomarkers for platinum resistance, such as FOXC1 (8) and Circ_0058063 (9). Other evidence also showed the subtype of BC is associated with response to chemotherapy (10). These biomarkers are insufficient for effective treatment decisions because these studies were conducted on a molecular or cellular level and lacked prognostic information. With the advancements in transcriptomics, incorporating various biomarkers as well as clinical data to construct a risk stratification model has become a viable option (11). Compared to single biomarker, integrating multiple predictive genes into a single system would enhance the robustness and prognostic accuracy. Many gene signatures for prognosis in BC have sprung out recently. Wang et al. identified seven immune-related lncRNAs signature: Z84484.1, AC009120.2, AL450384.2, AC024060.1, TNFRSF14-AS1, AL354919.2, OCIAD1-AS1 (12). Yang et al. reported nine genes signature based on ferroptosis: ALB, BID, FADS2, FANCD2, IFNG, MIOX, PLIN4, SCD, and SLC2A3 (13). However, as far as we know, a platinum resistance-related model has not been reported before.

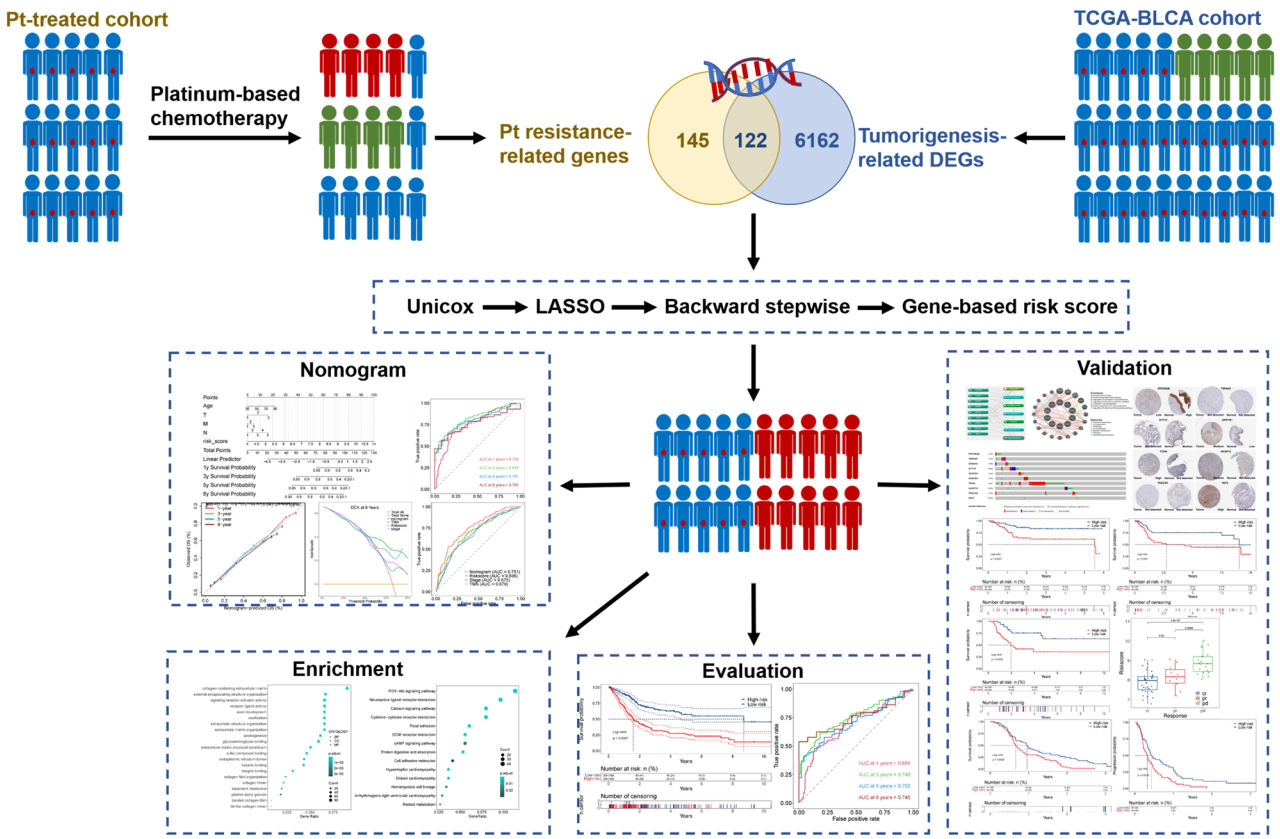
In this study, we aimed to identify essential bladder cancer-related genes involved in both platinum-based chemotherapy resistance and survival. Based on these genes, we established a risk score model and stratified patients into different risk groups. The robust prognostic ability of this model was verified in three independent BC datasets with platinum-based chemotherapy. Additionally, by integrating clinical features and risk score, a nomogram with enhanced prediction power was built. Besides, in an attempt to have a deeper understanding of this model, we used multiple databases to investigate the expression, functional interaction, and mutation of these genes. Enrichment analyses were carried out to further explore the possible mechanisms. As far as we know, this is the first prognostic model for predicting outcomes and discriminating responses to platinum-based chemotherapy in BC patients. Our model would play an important role in prognosis stratification and assisting individualized treatment.

MATERIALS AND METHODS

Data collection and preprocessing

The overall design of this study is shown in Figure-1. In training data, the RNA-seq data (Counts) with corresponding survival, phenotype, and clinical information of 411 BLCA (Bladder Urothelial Carcinoma) samples and 19 normal bladder tissues were collected from The Cancer Genome Atlas (TCGA) database (https://portal.gdc.cancer.gov/). Genes with low expression (the average expression < 1, or zero expression in more than 25% of samples) were excluded. Ensemble ID was converted to gene symbol by annotation file downloaded from the GENCODE website (https://www.gencodegenes.org/). In validation data, "bladder cancer" and "chemotherapy resistance" were used as the keywords for searching gene chips from the Gene Expression Omnibus (GEO) (https://www.ncbi.nlm.nih.gov/geo/). The inclusion criteria were as follows: (1) the biospecimens were gained from human primary bladder cells or tissues; (2) containing transcriptomic data; (3) including at least 10 samples in each group; (4) the survival information was available; (5) enrolling patients that had undergone platinum-based chemotherapy; (6) no previous or concomitant immunotherapy. Two independent GEO datasets (GSE13507 and GSE31684) (14-17) that meet our requirement were downloaded by "GEOquery" package (18). Entrez ID was converted to gene symbol according to platform files, only maximum expression was retained when multiple Entrez IDs were annota-

Figure 1 - The overall design of the current study. Pt: Platinum.



ted by same gene symbol. Detailed information about three datasets is shown in Table-S1 (Click here). Patients with progressive disease were defined as platinum resistance, while patients with partial response and complete response were defined as platinum sensitive.

Differentially expressed genes (DEGs)

The clinical information of patients enrolled was obtained by using "TCGAbiolinks" package (20-22), by focusing on those cases who undergone platinum-based chemotherapy, the acquired file contains 158 rows which were filtered to 100 unique samples, and 97 of them had corresponding gene expression data. The microarray data of samples with "Clinical Progressive Disease" and "Complete Response" therapeutic responses were imported into the "DESeq2" package (23), with a threshold of fold change > 2 or < 0.5, and adjust p value < 0.05, platinum resistance-related DEGs were defined. DEGs between primary tumor and normal samples were screened in the same way, meanwhile, the expression matrix was normalized, box plot proved batch effects among 430 samples were as well eliminated. Venn diagram depicting the intersection of platinum resistance-related DEGs and tumorigenesis-related DEGs in TCGA-BLCA dataset, those co-DEGs were retained for further Cox regression. Volcanic plots and heatmaps for DEGs were produced by "ggpubr" and "pheatmap" packages, respectively.

A gene-based prognostic model

The expression data were log2 transformed to make the hazard ratio more significant. Of the 411 cases, 406 unique tumor biospecimens have associated survival information. Based on a criterion that the statistical significance threshold is log-rank P value < 0.05, a set of DEGs that were significantly related to prognosis were derived from univariate Cox regression. "Glmnet" package (24, 25) was used for least

absolute shrinkage and selection operator (LASSO) Cox regression to subsequently select predictors, genes with non-zero coefficients were entered into backward stepwise regression. Finally, 10 optimal predictive genes and their coefficients were acquired, both Akaike's information criterion (AIC) value and the number of factors were all minimized. The risk score for each sample was calculated as follows:

Risk score = $\sum_{i=1}^{n} \beta i * Expi.$

where $\beta\iota$ stants for regression coefficient of gene *i, Expi* stands for the expression level of gene i. Forest plot outlined hazard ratios (HR) and confidence intervals of 10 genes, survival map of them was plotted by the GEPIA 2 website (http://gepia2.cancer-pku.cn). Multicollinearity among them was tested by variation inflation factors (VIF) and correlation coefficients.

Evaluating prognostic performance of gene-based model in training and validation groups

Univariable and multivariable Cox regression were performed to weigh up the predictive strength of risk score and other clinical parameters (age, gender, subtype, grade, stage, and TMN stage). Some characteristics which have very small numbers, for example, stage i, T0, and T1, were merged with their connected groups, and the results were summarized in forest plots. All patients in each dataset were classified into high-risk group and low-risk group, the cut-off points were based on median risk score (TCGA and GSE13507) or produced by X-tile software (GSE31684 and GSE14208). Survival risk differences between high- and low-risk groups were demonstrated by Kaplan-Meier survival analysis and log-rank test. Time-depended receiver operating characteristic (ROC) curves were applied to evaluate the prognostic performance of gene-based risk score with "TimeROC" package (26). Patients who have undergone platinum-based chemotherapy in TCGA and GSE13507 datasets were divided by their therapeutic responses, and boxplots were used for revealing the relationship between risk score and platinum resistance.

Building and estimation of nomogram

Based on "rms" package, salient clinical parameters in multivariate Cox regression and risk score were enrolled into a nomogram model to predict 1-, 3-, 5-, and 8-year overall survival (OS) of BC patients. The discriminatory capacity of the nomogram model was estimated by ROC curve, meanwhile quantified by area under the curve (AUC) and concordance index (C-index). Sensitivity and specificity of different models were compared by "plotROC" package. Calibration plot revealed predictive accuracy of nomogram by comparing predicted survival rate with observed survival rate at different time points, the value of resampling was set to 1000 to reduce overfitting. Decision curve analysis (DCA) illustrated clinical net benefit of the nomogram model and other prognostic indicators with "dcurves" package, which proved the clinical utility of the nomogram.

Functional enrichment and pathway analysis

We used "clusterProfiler" package (27) to reveal Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways analysis for risk groups. P-values were adjusted by Benjamini and Hochberg's approach in order to check false discovery rate (FDR), enriched biological functions and activated pathways with FDR < 0.05 were picked out, and the top of them were exhibited in dot plots. Besides, we performed gene set enrichment analysis (GSEA) by GSEA_4.2.3 software with 1000 permutations. The BioCarta, KEGG, and CGP subsets of curated gene sets (C2), GO subset of ontology gene sets (C5), and oncogenic signature gene sets (C6) were downloaded from Molecular Signatures Database (MSigDB, http://www.gsea-msigdb.org/gsea/msigdb/index.jsp) (28-31). Significance criteria were nominal p value < 0.05, FDG < 0.25, and |NES| > 1.

Co-occurrence analysis of chemotherapy resistance

COREMINE Medical website (http://www.coremine.com/medical) is a domain-specific information platform that mainly focused on biomedicine research and drug discovery. Employing text-mining, it allows users to navigate relationships among research contents from the latest published scientific literature. The

keywords of "neoplasms", "drug resistance", and "cisplatin" were combined with 10 genes as inputs into the search field for co-occurrence analysis, then a graphic network of them was generated.

Functional interaction network

GeneMANIA website (http://genemania.org) is a resource-rich tool for generating hypotheses about co-expression and functional interactions among genes (32). We imported the 10 genes in prognostic model into human database, 20 prioritized functionally similar genes were selected automatically, and a biological process weighted gene-gene network was constructed.

Immunohistochemistry analysis

The Human Protein Atlas (THPA) (https://www.proteinatlas.org) is a database focusing on genome-wide analysis of human proteins, which contains expression data and immunohistochemically (IHC) stained tissue images of each protein-coding gene, establishing a correlation between tumor development and specific gene expression of 17 major cancer types. The expression levels of 10 genes, as well as the subcellular localization of their products between urothelial cancer and normal bladder, were compared by IHC images downloaded from "Pathology" and "Tissue" sections of THPA website, respectively. For same gene, in order to make the result more comparable, we chose images generated by identical antibody from similar patients. We also obtained 5-year survival rate of high expression group and low expression group regarding each protein to validate their impact on cancer patient survival.

Gene mutation and copy number alteration

The cBioPortal (https://www.cbioportal.org) is a visualization tool for cancer genomics with large data sources (33, 34). It provides us an access to explore relationships between gene alteration and clinical features in specific cancer type or pan-cancer scope, and further explore the oncogenic mechanism at chromosomal level. We obtained the mutations and copy number alterations of 10 genes based on Bladder Cancer (MSK/TCGA, 2020) database, which incorporates 476 paired muscle-invasive bladder tumors and normal samples. The proportions of amplification, deep deletion, multiple alteration, and mutation were exhibited in stacked column charts.

Quantification of immune cell infiltration

We applied CIBERSORTx (https://cibersortx.stanford.edu) to quantify the constitution of 22 human leukocyte types by using non-negative matrix factorization (NMF) algorithm (35, 36). The different infiltration degrees of immune cells in high-risk group and low-risk group were revealed in violin plot. Furthermore, for macrophages M0 and M2 that may have potential effect on antitumor treatment resistance, the correlation of risk score and their fractions were assessed by linear regression.

Statistical analysis

Statistical analysis was carried out using R software (version 4.1.3; https://www.R-project.org/). Differences among GEO datasets and TCGA dataset were accessed by One-way Analysis of Variance (ANOVA) and Wald test, respectively. For continuous variables, differences between two groups were examined by Wilcoxon-Mann-Whitney (WMW) test or Student's t-test. For categorical variables, Chi-square test or Fisher's exact test were used to analyze assumptions depending on the proportion of groups that contain less than 5 patients. P-value < 0.05 was a statistical significance threshold for all analyses, with $p < 0.1$, $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$.

RESULTS

Screening of platinum-based chemotherapy resistance-related genes

By using transcriptomic data of urothelium carcinoma samples that had undergone platinum--based chemotherapy in TCGA database, 267 DEGs between different therapeutic responses were confirmed, including 81 up-regulated and 186 down--regulated genes. Then, with all 430 samples in TCGA-BLCA database, 6284 DEGs were screened

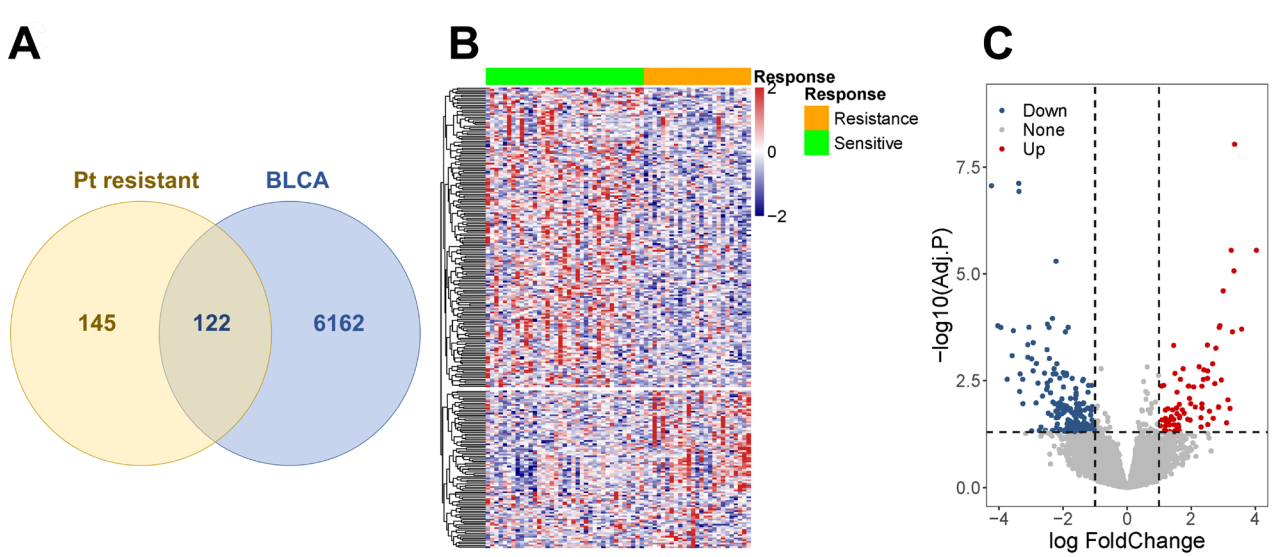
(Table-S2) (Click here). Venn diagram (Figure-2A) depicted 122 co-DEGs in these two cohorts. Heatmaps and volcano plots exhibited tumorigenesis--related (see appendix-1 - Figure-S1 A and B) and platinum-based chemotherapy resistance-related DEGs (Figure-2 B and C), respectively. Box plot (see appendix-1 Figure-S1 C) revealed the homogeneity of each sample after normalization.

Identification of 10 genes with best predictive value

Thirty seven DEGs that were significantly associated with the overall survival of BC patients were selected by univariate Cox regression ($p < 0.05$, Table-S3) (Click here). LASSO Cox regression was used to reduce dimensions and prevent excessive fitting (see appendix-1 Figure-S2 A and B), and 21 DEGs were picked out (lambda = 0.018). After verifying the proportional hazard assumption, 10 genes with best predictive value were determined by backward stepwise regression: PPP2R2B, TSPAN7, ATAD3C, SYT15, SAPCD1, AKR1B1, TCHH, AKAP12, AGLN3, and IGF2. Hazard ratios (HRs) and confidence intervals of them are shown in forest plot (see appendix-1 Figure-S3).

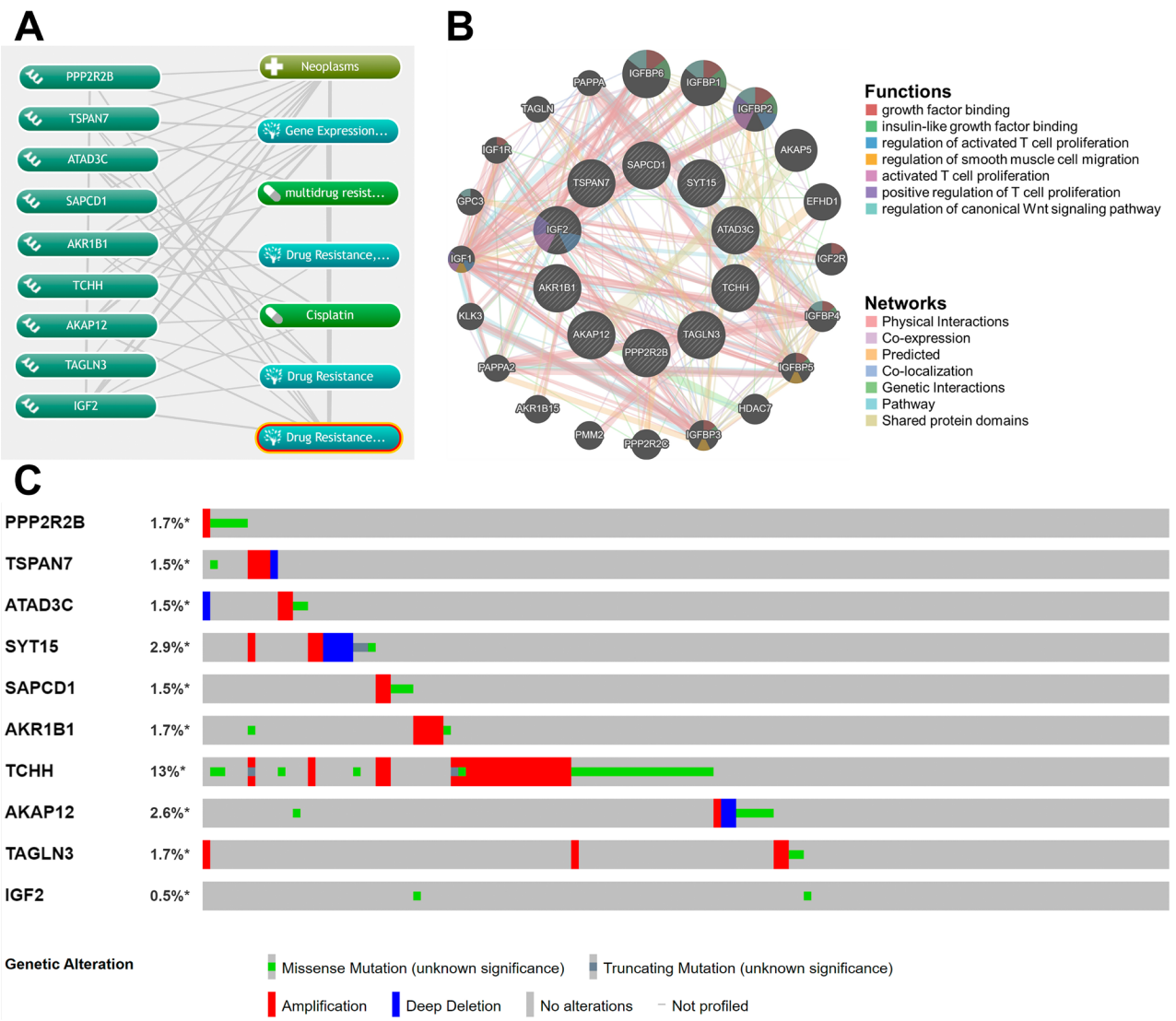
We consulted the COREMINE Medical website about these genes. The results exhibited that, except for SYT15, the remaining 9 genes participate in oncogenicity and platinum-based chemotherapy resistance directly or indirectly (Figure-3A). Functional interaction, co-expression, biological process annotation, and gene-gene networks among these 10 genes were acquired from GeneMANIA website (Figure-3B). Additionally, Figure-3C elucidates the mutation type and ratio of each gene, 81 (18%) of 438 sequenced samples/patients have at least one alteration regarding 10 genes. To explore the gene expression on a protein level, we extracted immunohistochemistry (IHC) images of urothelial cancer and normal bladder samples regarding each gene (see appendix-1 Figure-S4). Among genes recorded in "Pathology" section in THPA, staining intensities of AKR1B1, TCHH, AKAP12, and IGF2 are distinctly higher in tissues from urothelial carcinoma than in normal bladder. PP2R2B and STY15 have evidently lower expression levels in bladder tumors versus non--cancerous tissues. Neither TSPAN7 nor TAGLN3 was detected by antibodies used in IHC staining. What is more, for gene that has elevated staining intensity in cancer cells, the 5-year survival rate of high expression group was worse compared

Figure 2 - Differentially expressed genes of platinum-treated cohort in TCGA-BLCA dataset.



Heatmap (A) and volcano plot (B) of platinum-based chemotherapy resistance-related DEGs. Heatmap (A) and volcano plot (B) of platinum-based chemotherapy resistance-related DEGs. red color represented up-regulated genes with $p < 0.05$ and log FC > 1, blue color represented down-regulated genes with $p < 0.05$ and log FC < -1. (C) Venn diagram of 122 co-DEGs between whole TCGA-BLCA cohort and platinum-based chemotherapy treated cohort.

Figure 3 - Co-occurrence, functional interaction, and copy number alteration of 10 genes.



(A) Relationship among neoplasms, chemotherapy resistance, and prognostic genes. (B) The gene-gene interaction network and biological process annotation. (C) Mutations and copy number alterations of 10 genes. red part indicates amplification, blue part indicates deep deletion. PPP2R2B: protein phosphatase 2 regulatory subunit Bbeta; TSPAN7: tetraspanin 7; ATAD3C: ATPase family AAA domain containing 3C; SYT15: synaptotagmin 15; SAPCD1: suppressor APC domain containing 1; AKR1B1: aldo-keto reductase family 1 member B; TCHH: trichohyalin; AKAP12: A-kinase anchoring protein 12; TAGLN3: transgelin 3; IGF2: insulin like growth factor 2.

with that of low expression group, and vice versa (Table-S4). (Click here). These all together were consistent with HRs of each gene in stepwise regression.

A gene-based prognostic model

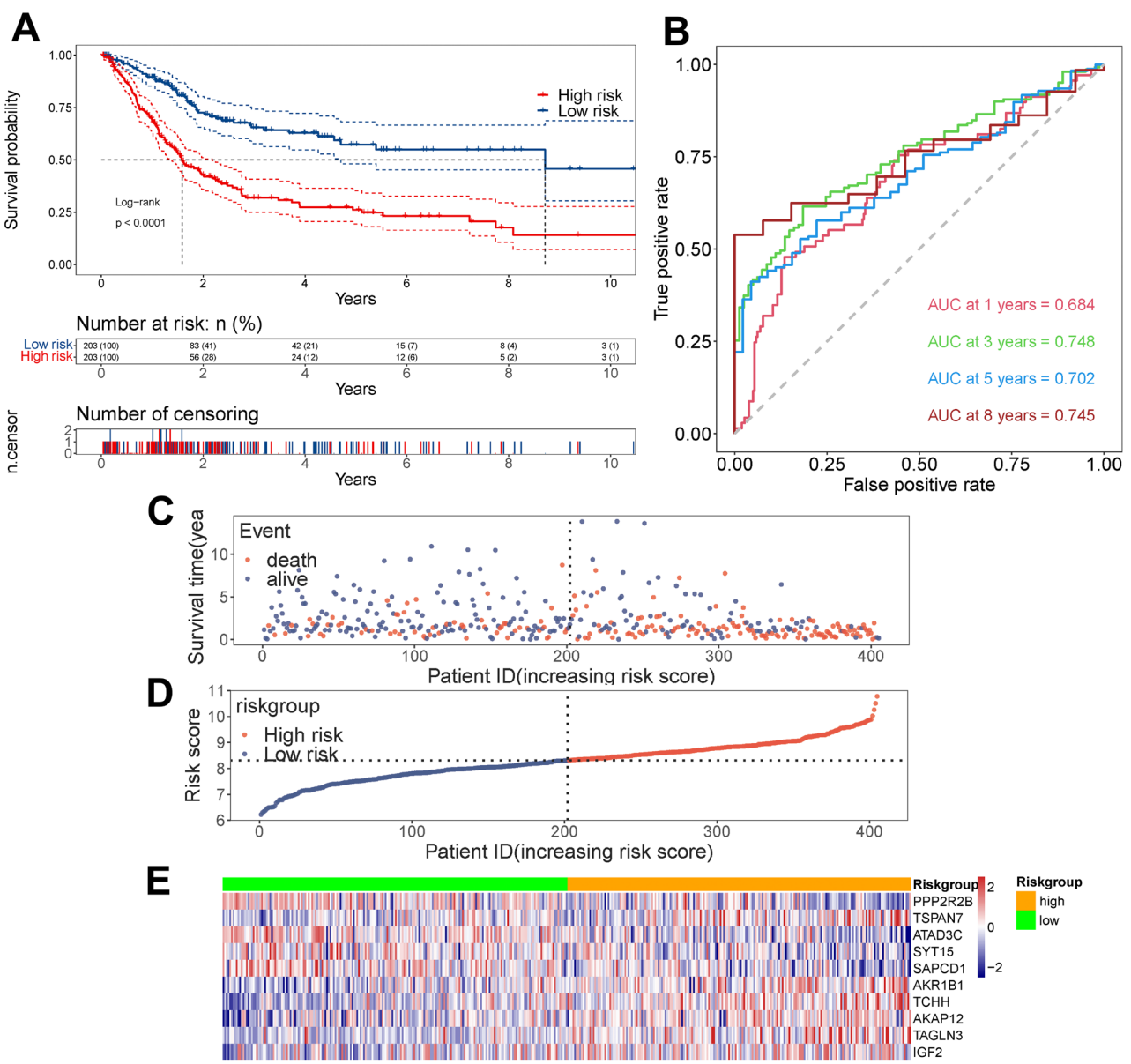
Through the above steps, we identified 10 platinum resistance-related genes with prognostic value in bladder urothelial carcinoma. In order to investigate the prognosis effect of 10 genes as a whole, we computed risk scores for every patient based on regression coefficients as follows:

$$risk\ score = -0.354 * Exp_{PPP2R2B} + 0.770 * Exp_{TSPAN7} - 0.650 * Exp_{ATAD3C} - 0.451 * Exp_{SYT15} - 0.547 * Exp^{SAPCD1} + 1.558 * Exp_{AKR1B1} + 0.468 * Exp_{TCHH} + 0.459 * Exp_{AKAP12} + 0.288 * Exp_{TAGLN3} + 0.644 * Exp_{IGF2.}$$

All patients in training dataset (TCGA-BLCA dataset) were divided into high-risk group and

low-risk group based on the median risk score as critical value. Kaplan-Meier (K-M) plot showed a significantly enhanced overall survival of low-risk group than high-risk group ($p < 0.0001$; Figure--4A), the median survival time for low-risk group is 8.7 years and for high-risk group is 1.6 years. This gene-based risk score model yielded an area under the curve (AUC) of 0.684, 0.748, 0.702, and 0.745 in 1-, 3-, 5-, and 8-year survival prediction, respectively (Figure-4B), by its satisfactory predictive accuracy. Clinical features of patients were summarized in Table-1, the high-risk group was associated with non-papillary subtype, lower survival rate, shorter lifetime, and advanced disease

Figure 4 - Evaluating prognostic performance of gene-based model in training group.



(A) Survival analysis of TCGA-BLCA dataset. patients were divided into high-risk group and low-risk group based on median risk score. (B) Time-dependent ROC curves show the performance of risk score in predicting 1-, 3-, 5-, and 8-year OS in TCGA-BLCA dataset. (C) Risk score curve of high- and low- risk groups in TCGA-BLCA dataset. patients were listed in an order of increased risk scores; the dotted line represents cut-off value of risk score that divides patients into two groups. (D) Survival status of high- and low- risk groups in TCGA-BLCA dataset. (E) Heatmap shows the expression of 10 prognostic genes in high- and low- risk groups.

Table 1. Clinical features of BC patients in TCGA dataset.

Clinical features	BC patients	Low-risk group	High-risk group	p-value
Patients, no (%)	406 (100)	203 (50)	203 (50)	
Median age (years)	68.5	66	70	
Gender, no (%)				0.572
Female	106 (26.1)	50 (24.6)	56 (27.6)	
Male	300 (73.9)	153 (75.4)	147 (72.4)	
Stage, no (%)				< 0.001
Stage i + ii	131 (32.3)	84 (41.4)	47 (23.2)	
Stage iii	141 (34.7)	68 (33.5)	73 (36.0)	
Stage iv	132 (32.5)	49 (24.1)	83 (40.9)	
Unknown	2 (0.5)	2 (1.0)	0 (0)	
Grade, no (%)				0.004
Low grade	20 (4.9)	15 (7.4)	5 (2.5)	
High grade	383 (94.3)	186 (91.6)	197 (97.0)	
Unknown	3 (0.7)	2 (1.0)	1 (0.5)	
Subtype, no (%)				< 0.001
Papillary	131 (32.3)	89 (43.8)	42 (20.7)	
Non-Papillary	270 (66.5)	113 (55.7)	157 (77.3)	
Unknown	5 (1.2)	1 (0.5)	4 (2.0)	
Pathologic T, no (%)				< 0.001
T0 + T1 + T2	122 (30.0)	72 (35.5)	50 (24.6)	
T3	193 (47.5)	81 (39.9)	112 (55.2)	
T4	58 (14.3)	26 (12.8)	32 (15.8)	
Unknown	33 (8.1)	24 (11.8)	9 (4.4)	
Pathologic M, no (%)				0.004
M0	198 (48.8)	115 (56.7)	83 (40.9)	
M1	11 (2.7)	3 (1.5)	8 (3.9)	
Unknown	197 (48.5)	85 (41.9)	112 (55.2)	
Pathologic N, no (%)				0.003
N0	236 (58.1)	126 (62.1)	110 (54.2)	
N1	44 (10.8)	13 (6.4)	31 (15.3)	
N2	76 (18.7)	33(16.3)	43 (21.2)	
N3	7 (1.7)	2 (1.0)	5 (2.5)	
Unknown	43 (10.6)	29 (14.3)	14 (6.9)	
Status, no (%)				< 0.001
Alive	226 (55.7)	146 (71.9)	80 (39.4)	
Dead	180 (44.3)	57 (28.1)	123 (60.6)	
Median survival (days)	536	603	455	

BC: Bladder cancer; TCGA: The Cancer Genome Atlas.

(a higher stage, grade, and pathological TMN stages). In addition, we estimated the distribution of risk scores in OS and OS status. By listing patients in an order of increased risk scores (Figure-4C), we observed a worse survival in high-risk group (decreased in OS and increased number of deaths; Figure-4D). Heatmap of 10 genes displayed the trend of their expression levels with elevated risk scores (Figure-4E). For the purpose of exploring the intervention effects of different clinical characteristics and whether risk score works better for patients with certain conditions, we worked with subgroup analysis by breaking down all study samples into subsets based on age, gender, subtype, grade, stage, and pathological TMN stages. Prognosis of patients with high risk scores were poorer than patients with low risk scores in age < 68 ($p < 0.0001$), age ≥ 68 ($p < 0.0001$), female ($p = 0.003$), male ($p < 0.0001$), subtype of papillary ($p = 0.00048$), subtype of non-papillary ($p < 0.0001$), high grade ($p < 0.0001$), stage ii ($p = 0.015$), stage iii ($p < 0.0001$), stage iii+iv ($p < 0.0001$), stage iv ($p = 0.017$), pathological stage of T2 ($p = 0.087$), pathological stage of T3 ($p < 0.0001$), pathological stage of T3+T4 ($p < 0.0001$), pathological stage of T4 ($p = 0.0036$), pathological stage of M0 ($p < 0.0001$), pathological stage of Mx ($p < 0.0001$), pathological stage of N0 ($p < 0.0001$), and pathological stage of N1+N2+N3 ($p = 0.037$), the K-M plot and AUC of each subgroup were shown in appendix-1 Figure-S5.

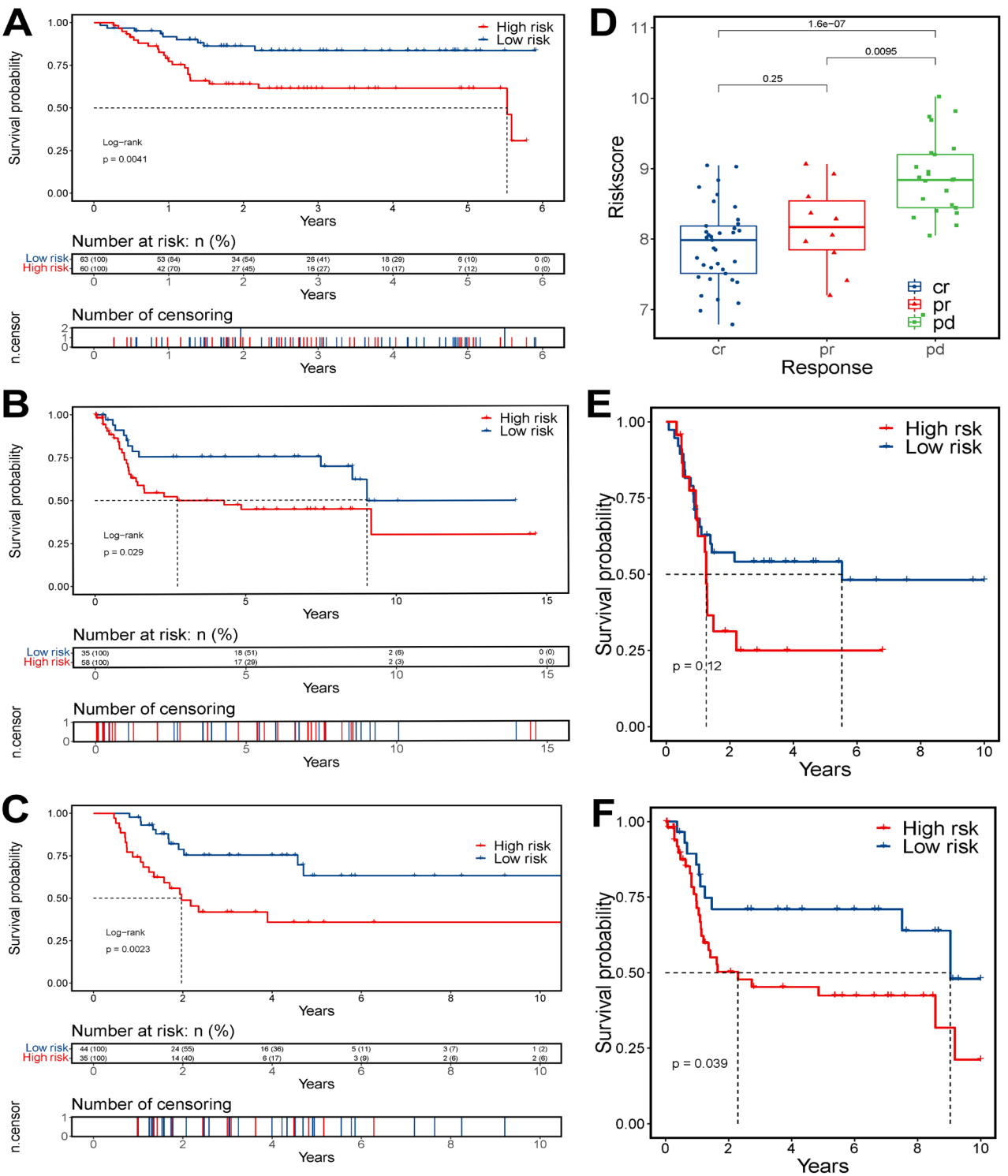
Predictive ability of risk score in validation datasets

The robust predictive ability of this gene-based risk score was validated in GSE13507 (Figure-5A), GSE31684 (Figure-5B), and a subset of patients who had undergone platinum-based chemotherapy in TCGA-BLCA dataset (Figure-5C). K-M plots of three databases showed that patients in low-risk group have better prognoses than patients in high-risk group ($p = 0.0041$, 0.029, and 0.0023, respectively). The time-dependent ROC curves possessed AUC values of 0.727 and 0.718 in predicting 3- and 5-year survival for GSE13507 (see appendix-1 Figure-S6A), 0.61 and 0.658 in predicting 3- and 8-year survival for GSE31684 (Figure-S6B), 0.841, 0.766, 0.707, 0.661 in predicting 1-, 3-, 5-, and 8-year survival for platinum-based chemotherapy-treated patients in TCGA-BLCA dataset (see appendix-1 Figure-S6C), respectively. Aiming to display the correlation between risk score and the sensitivity to platinum-based chemotherapy, we grouped platinum-treated patients in TCGA-BLCA dataset into three subsets according to their therapeutic response, risk scores of patients with "clinical progressive disease (pd)" after chemotherapy were significantly higher than patients in "partial response (pr)" group ($p = 0.0095$) and "completely response (cr)" group ($p < 0.0001$; Figure-5D). Then we used similar methods in GSE13507, patient who was sensitive to cisplatin generated a lower risk score than patient who was resistant to cisplatin (see appendix-1 Figure-S6D), suggesting that risk score is a predictor of decreased chemosensitivity. Furthermore, given that patients with less than T2 disease are not usually included in platin-based systemic treatment, the survival analyses were performed in patients from T2 or above T2 subgroups in GSE13507 (Figure-5E) and GSE31684 (Figure-5F). In these subgroups of two datasets, consistent with previous results, patients in low-risk group still had a better prognosis. The survival difference was not significant in the first year in GSE13507 ($p=0.12$), which may due to the interference of other comorbidities. The distribution of risk scores and survival status of GSE13507 was shown in (see appendix-1 Figure-S6E).

Developing and evaluating the prediction nomogram

Univariate Cox regression proved that age, stage, pathological T, M, N, and risk score were salient prognostic indicators ($p < 0.05$; Figure-6A), followed by multivariate Cox regression to test their independency (Figure-6B). Based on results of regressions, age, pathological T, M, and N were combined with gene-based risk score to develop a prediction model with nomogram, which was able to work out numerical probabilities of 1-, 3-, 5-, and 8-year overall survival (Figure-6C). The performance of nomogram was first examined by ROC analysis (Figure-6D). The concordance index (C-index) of nomogram was 0.727, and AUC of predicting 1-, 3-, 5-, and 8-year survival rates

Figure 5 - Evaluating prognostic performance of gene-based model in validation group.



Survival analysis of GSE13507 (A), GSE31684 (B), and platinum-based chemotherapy treated patients in TCGA-BLCA dataset (C). (D) Boxplot reveals the correlation between risk score and response to platinum-based chemotherapy in TCGA-BLCA dataset; cr: completely response; pr: partial response; pd: clinical progressive disease. K-M plots reveals the survival of patients with T2 or above T2 disease in GSE13507 (E) and GSE31684 (F).

could reach 0.752, 0.819, 0.797, and 0.765, respectively. Then, in calibration plot, broken lines proximately coincide with the diagonal line, confirming the predictive accuracy of nomogram (Figure-6E). Decision curve analyses (DCA) in predicting 3- (see appendix-1 Figure-S7A), 5- (see appendix-1 Figure-S7B), and 8-year survival rates (Figure-6F) were conducted to determine whether a judgment method could enhance clinical decision at a specific threshold. The curve of nomogram (green) generated the greatest net benefit, followed by risk score, declaring their excellent clinical utility. Besides, this result also illustrated that the incorporation of gene-based risk score could enhance predictive performance. From the comparation of predictive abilities among nomogram, risk score, stage, and pathological TMN stages, both AUC (0.751; Figure-6G) and specificity (85.2%; Table-2) of nomogram outperformed other clinical characteristics, proving its prognostic value.

GO, KEGG, and GSEA

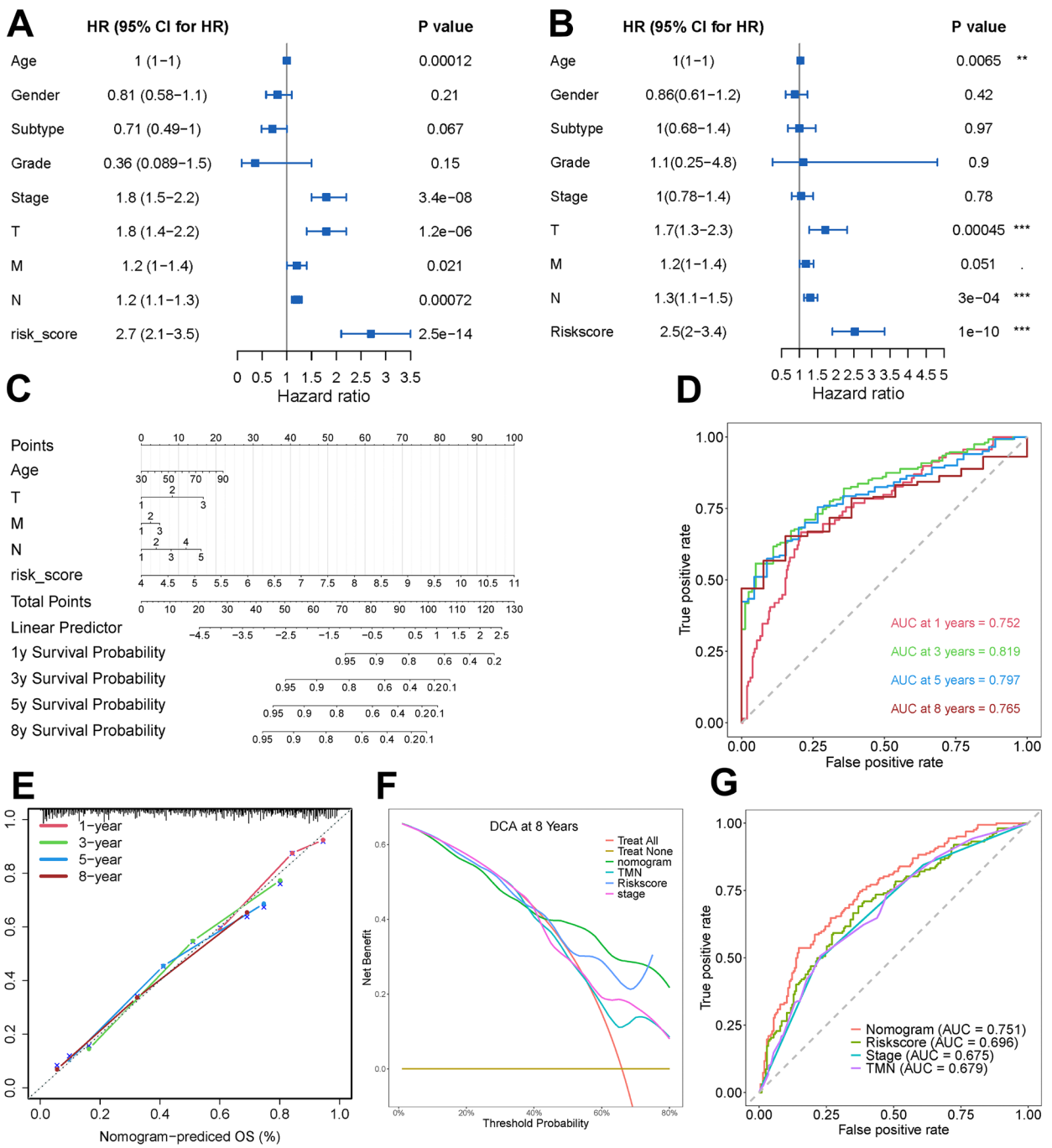
One thousand two hundred ninety-nine DEGs between high-risk group and low-risk group were defined, including 847 up-regulated genes and 452 down-regulated genes (Figure 7 A and B). The molecular characteristics and pathways of risk score were investigated by enrichment analysis. For biology process (BP), cell component (CC), and molecular function (MF) categories in GO analysis, the top 7 significantly enriched by risk score in each category were displayed in dot plot (Figure-7C). For KEGG analysis, 14 pathways were significantly enriched (FDR < 0.05; Figure-7D). Those terms were principally concentrated in extracellular matrix structural constituent, fibrillar collagen organization, cell-cell adhesion, signaling transmission pathway of PI3K and Calcium, which were consistent with the results of GSEA (Table-S5). (Click here). In oncogenic signatures, angiogenesis factors (VEGF, PDGF, and PGF),

Table 2 - Comparison of prediction performance among different models.

Models	AUC	95% CI	SE	Sensitivity (%)	Specificity (%)	p-value
Risk score	0.696	0.642-0.750	0.028	69.1	63.1	< 0.001
1-year	0.684	0.608-0.759	0.038			
3-year	0.748	0..685-0.812	0.032			
5-year	0.702	0.625-0.779	0.039			
8-year	0.745	0.651-0.838	0.048			
Nomogram	0.751	0.701-0.801	0.025	53.7	85.2	< 0.001
1-year	0.752	0.687-0.818	0.033			
3-year	0.819	0.764-0.873	0.028			
5-year	0.797	0.732-0.863	0.033			
8-year	0.765	0.671-0.859	0.048			
Stage	0.675	0.623-0.727	0.026	48.8	78.3	< 0.001
TMN	0.679	0.625-0.734	0.028	50.6	77.3	< 0.001

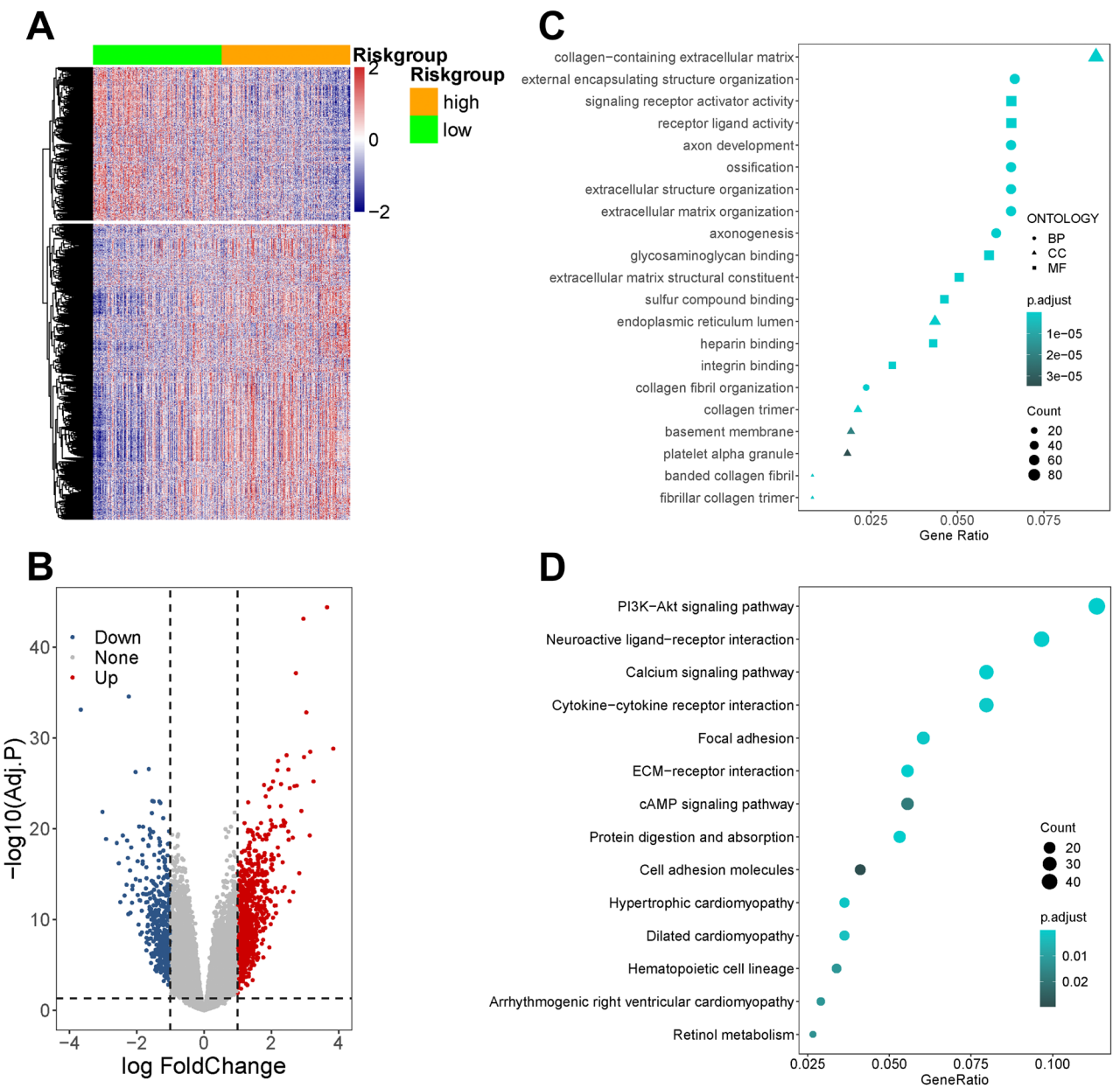
AUC = Area under the curve; CI = Confidence interval; SE = Standard error; TMN = The pathological T, M and N stages of tumor.

Figure 6 - Building and estimation of nomogram.



Forrest plots summarized the results of univariate Cox regression (A) and multivariate Cox regression (B) for risk score and other clinical characteristics, T, M, and N stood for pathological T, M, and N stages. (C) Nomogram for predicting 1-, 3-, 5-, and 8-year survival rate in TCGA-BLCA dataset. Time dependent ROC curves (D) and calibration plot (E) used to analyze the performance of nomogram in predicting 1-, 3-, 5-, and 8-year survival rates. (F) Decision curve analysis (DCA) demonstrated the utility of nomogram in predicting 8-year survival rate. (G) ROC curves compared the predictive performances of different models.

Figure 7 - Functional enrichment and pathway analysis.



Heatmap (A) and volcano plot (B) of DEGs between high- and low- risk groups. Dot plots of GO (C) and KEGG (D) enrichment analysis for risk score.

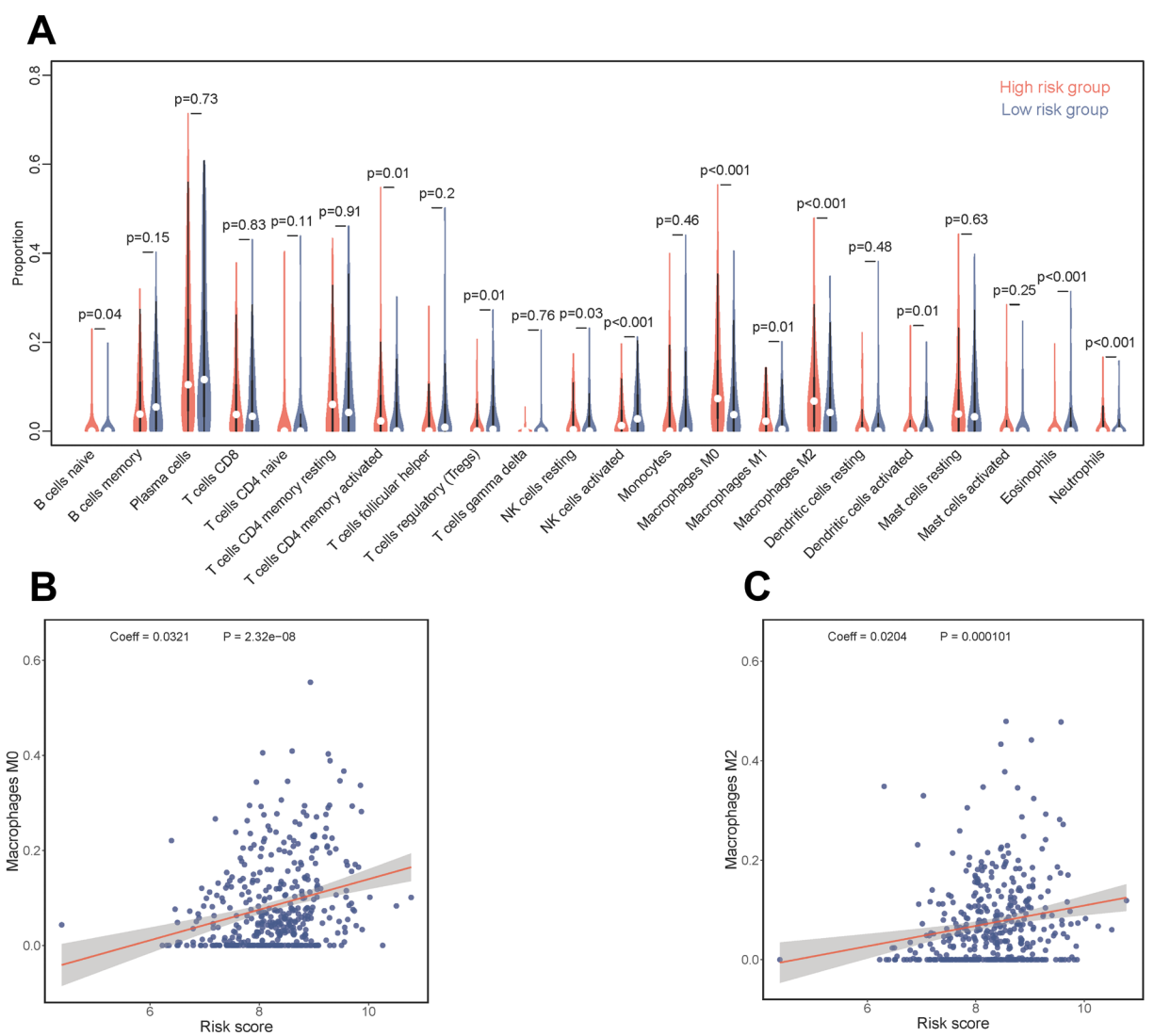
mTOR signaling pathway, E2F1 transcriptional factor, polycomb repressive complex 2 (PRC2), cAMP, and KRAS were enriched by high-risk score, while p53 was downregulated. Implying the close association of gene-based risk score with the occurrence, development, and metastasis of tumor.

Correlation between risk score and tumor immune infiltrating cells (TICs)

The relationship between risk group and immune cells infiltration were analyzed using CIBERSORTx database. Results presented the proportion of macrophages M0 ($p < 0.001$) and M2 ($p < 0.001$) were elevated in high-risk group (Figure-8A). Linear regression further revealed that the immune infiltration levels of macrophages M0 (Coeff = 0.032, $p < 0.001$) and M2 (Coeff = 0.020, $p < 0.001$) were positively correlated with risk scores (Figures 8 B and C).

DISCUSSION

Figure 8 - Quantification of immune cell infiltration.



(A) Violin plot of 22 subpopulations of tumor immune cells infiltration between high- and low-risk group in TCGA-BLCA cohort. Scatter plot of the correlation between risk score and proportion of macrophages M0 (B) and M2 (C) cells.

BC is a biologically diverse disease and progresses to multiple clinical outcomes. Especially for MIBC, which is more aggressive, with a higher acquisition of genomic instability and mutation rate (37). The present grading and staging system for BC mainly depends on radiography or pathology, which evaluates the prognosis by tumor infiltration depth instead of biological characteristics. This is insufficient for predicting tumor progression, migration, and therapeutic sensitivity (38). Among variety of medicines, Platinum-based chemotherapy is the first-line treatment in systematic treatment for MIBC (39). But, platinum resistance remains a challenging issue. Genetic biomarkers would be viable to represent heterogeneity among BC, predicting the sensitivity of urothelial neoplasms tissues toward platinum. Previous studies have reported several prognostic gene signatures that are related to tumor microenvironment, immune cell infiltrating, unfolded protein response, and so on (40-42). However, signature associated with platinum-based chemotherapy resistance has not been recorded yet. Invigored by this, we attempted to identify a series of genes that were able to discriminate the platinum-based therapeutic benefits as well as predict the outcome of BC patients.

In the current study, we combined a variety of regression analyses, ten essential genes (PPP2R2B, TSPAN7, ATAD3C, SYT15, SAPCD1, AKR1B1, TCHH, AKAP12, AGLN3, and IGF2) that participating in both platinum-based chemotherapy resistance and survival were selected, then a prognostic model enrolling these genes was established. The risk score did well in stratifying patients into different risk groups, patients in low--risk group experienced a considerable survival advantage compared to those with a higher risk score. Cox regression showed the negative correlation between risk score and OS (HR = 2.7, $p < 0.0001$). Based on risk score and salient clinical features, a nomogram was generated to present the survival rate graphically. The nomogram model could yield a C-index of 0.727 and an AUC value up to 0.819. DCA and calibration curves also proved its promising prognostic ability. As shown in DCA, by incorporating risk score, the predictive power of clinical characteristics was strengthened. The stability and reproducibility of risk score were examined in other three independent BC datasets including cisplatin-treated patients. Moreover, a high-risk score was significantly associated with platinum resistance in BC patients. All together indicated the potential value of our model in clinical decision about platinum sensitivity and overall survival.

Among those ten genes, TSPAN7 and IGF2 have previously been reported to participate in bladder cancer progression and might be potential therapeutic targets. TSPAN7 exerts an anti-tumor effect via the PTEN/PI3K/AKT pathway in urothelial carcinoma (43). IGF2 participates in cell survival, growth and reproducing, and is overexpressed in variety of malignancies. IGF2 could contribute to anti-tumor therapy based on its regulation, modification, and downstream signaling way. IGF2 regulates PI3K/AKT/mTOR signaling pathway, targeting on IGF2 is a new therapeutic strategy for bladder cancer, and obstructing IGF2 signaling way could make cancer cell reacquire sensitivity to Taxol. Besides, among four kinds of IGF2 promoters, IGF2-P3 and IGF2-P4 have a high expression in bladder tumor tissues compared with normal bladder, which confirming their values in target therapy (44, 45).

In addition, most genes in our model were involved in the signaling pathways regulation in other kinds of cancer. In breast cancer, the expression level of PPP2R2B is significantly correlated with a longer distant metastasis-free survival and recurrence-free survival. Downregulation of PPP2R2B reduces the effect of trastuzumab or lapatinib on mTOR signaling, thus weaken the anti--HER2 sensitivity (46). What is more, PPP2R2B also involves in polarization of macrophages, the dysregulation of PPP2R2B would promote macrophages polarizing to M2, facilitating the immune evasion (47). Although TSPAN7 is an anti-tumor factor in bladder cancer, it promoted lung cancer progression by inhibits the expression of E--cadherin and vimentin, which raises the level of N-cadherin (48). It also has an interaction with the activation of β1 integrin-mediated downstream FAK-Src-Ras-ERK1/2 signaling pathway in oste-

osarcoma (49), boosting the cell epithelial-mesenchymal transition (EMT) process, indicating that the mechanisms of this gene and its downstream products still need to be explored. In lung cancer, AKR1B1 is a STAT3 activator that promotes glutathione de novo synthesis, eliminates ROS, protects cell from death, and reduces EGFR TKI drug sensitivity by upregulating the cystine transporter SLC7A11, it would be a therapeutic target for dealing with EGFR TKI resistance (50). TCHH methylation might play a potential role in the induced pluripotent stem cell (iPSC) differentiation, a higher level of TCHH methylation is observed in colorectal cancer liver metastasis sites and exhibits an association with tumor volume (51). Inspired by the multiple roles of these genes in other neoplasms, we carried on an analysis to 123 cisplatin-treated metastatic gastric cancer patients (GSE14208) used our risk score model, low-risk group exhibited better clinical outcomes than high-risk group not only in overall survival but also in progression-free survival, proving the robustness of our prognostic model.

To delineate the molecular mechanisms underlying the risk score, we executed enrichment analyses. GO and KEGG revealed that the risk score might play its role in extracellular matrix remodeling and cell-cell adhesion, which play an important role in tumor progression and metastasis. GSEA confirmed a significantly reduced p53, together with an elevated level of angiogenesis, histone methylation, silk/threonine kinase, cAMP, and K-ras gene in high-risk group. Many studies have stressed the role of these terms in chemotherapy resistance. For example, RAS and p53 promote or inhibit cisplatin resistance via regulate cellular apoptosis and autophagy in the opposite direction (52). Furthermore, the high-risk score was significantly associated with increased tumor infiltration of macrophages. Tumor-associated macrophages (TAMs) are crucial part of tumor immune microenvironment (TIME). Macrophages would be polarized to two phenotypes (M1 and M2), M1 suppresses tumor while M2 boosts tumor development. Exosomes derived from M2 have been shown to contribute to cisplatin resistance (53), and a repolarization of M2 to M1 would be a strategy to restore sensitivity toward platinum (54). These results denoted the reliability association between risk score and platinum sensitivity. Our model might have a practical value for prognosis stratification and early determination of therapeutic benefits.

However, our study also has some limitations. First, on account of the insufficiency of data resources, the platinum resistance-related DEGs were picked from one RNA-seq dataset (TCGA-BLCA dataset), it would be better if we could integrate transcriptomic data from more datasets. Second, we only know those patients had undergone platinum-based chemotherapy, but the exactly therapeutic strategies, such as GC or ddMVAC, were inaccessible to us. The mechanisms of these resistance might contain other than platinum therapy. Third, other information like blood and urine composition analyses, dietary habits, and lifestyle, is unclear. Forth, the proportion of patients that have undergone platinum-based chemotherapy and have definitive records of therapeutic response is relatively small, the inclusion of more eligible patients would be helpful to enhance reliability of our results. Fifth, as all conclusions in this study were processed through bioinformatics, additional biological experiments and multicenter clinical trials will assist in investigating the function of the 10 genes, as well as testing the prognostic ability in the actual world. Despite above limitations, this is the first prognostic model derived from platinum resistance and tumorigenesis, which could transform gene expression matrix into risk score and powerfully stratify patients into different prognostic groups. Bringing age and TMN stages into our model would further boost the predictive capacity. What is more, the clinical risk judgment based on an objective score system accompanied by a nomogram could also reduce the deviation arising from subjective factors of observers. All above demonstrated that our gene-based risk score model has satisfying potential of predicting platinum therapeutic effect and it could assist in conducting personalized treatment.

CONCLUSIONS

In summary, we identified a gene-based risk score model for bladder cancer patients that has clinical prognostic value not only in survival but also in platinum-based chemotherapy sensitivity. This finding has reference value to clinical treatment decisions and deepens our understanding of platinum-based chemotherapy resistance.

ABBREVIATIONS

BC = bladder cancer;
BLCA = bladder urothelial carcinoma;
MIBC = muscular invasive bladder cancer;
NMIBC = non- muscular invasive bladder cancer;
TCGA = The Cancer Genome Atlas;
GEO = Gene Expression Omnibus;
DEGs = differentially expressed genes;
OS = overall survival;
RFS = recurrence-free survival;
PFS = progression-free survival;
LASSO = least absolute shrinkage and selection operator;
AIC = Akaike's information criterion;
HR = hazard ratio;
VIF = variation inflation factors;
ROC - receiver operating characteristic;
AUC = area under the curve;
C = index: concordance index;
DCA = Decision curve analysis;
GO = Gene Ontology;
KEGG = Kyoto Encyclopedia of Genes and Genomes;
FDR = false discovery rate;
GSEA = gene set enrichment analysis;
THPA = The Human Protein Atlas;
IHC = immunohistochemistry;
TMN = The pathological T, M and N stages of tumor punctuation

DATA AVAILABILITY

The public transcriptomic datasets presented in this study are available in The Cancer Genome Atlas (TCGA) database (https://portal.gdc.cancer.gov/) and the Gene Expression Omnibus (GEO) (https://www.ncbi.nlm.nih.gov/geo/). Other information can be found in online repositories regarding names or links listed in the Materials and methods section. The data generated during the current study are presented in supporting information or available from authors on reasonable request.

FUNDING STATEMENT

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ETHICS APPROVAL AND CONSENT TO PARTICIPATE

TCGA and GEO belong to public databases with open source, patients enrolled in database have obtained ethical approval. Users can download relevant data from database for free for research and publish articles.

ACKNOWLEDGMENTS

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CONFLICT OF INTEREST

None declared.

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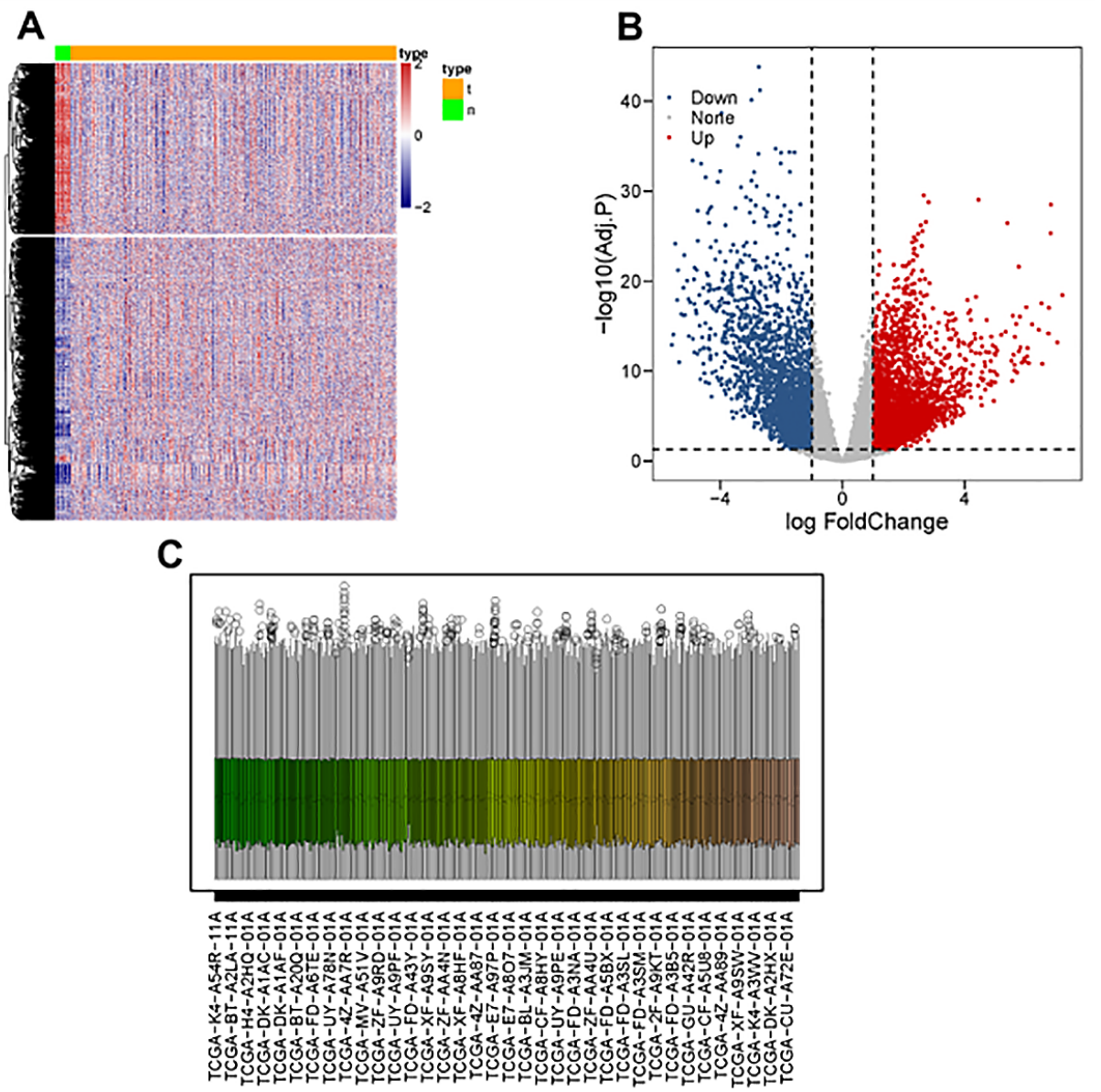
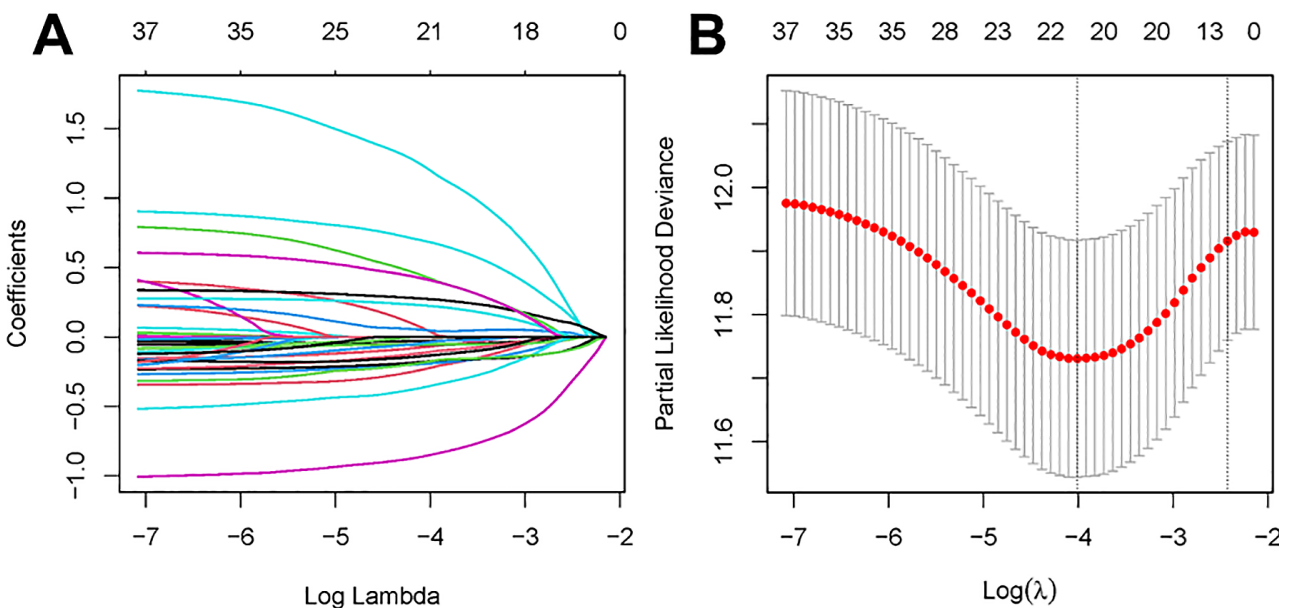
APPENDIX 1

Figure S1. Differentially expressed genes of TCGA-BLCA cohort.



Heatmap (A), Volcano plot (B), Box plot (C) of 430 samples in TCGA-BLCA after normalization by DESeq2 package.

Figure S2. The LASSO regression.



(A) LASSO coefficient profiles of 21 DEGs, (B) partial likelihood deviance versus log (λ).

Figure S3. Forest plot of 10 genes in prognostic model.

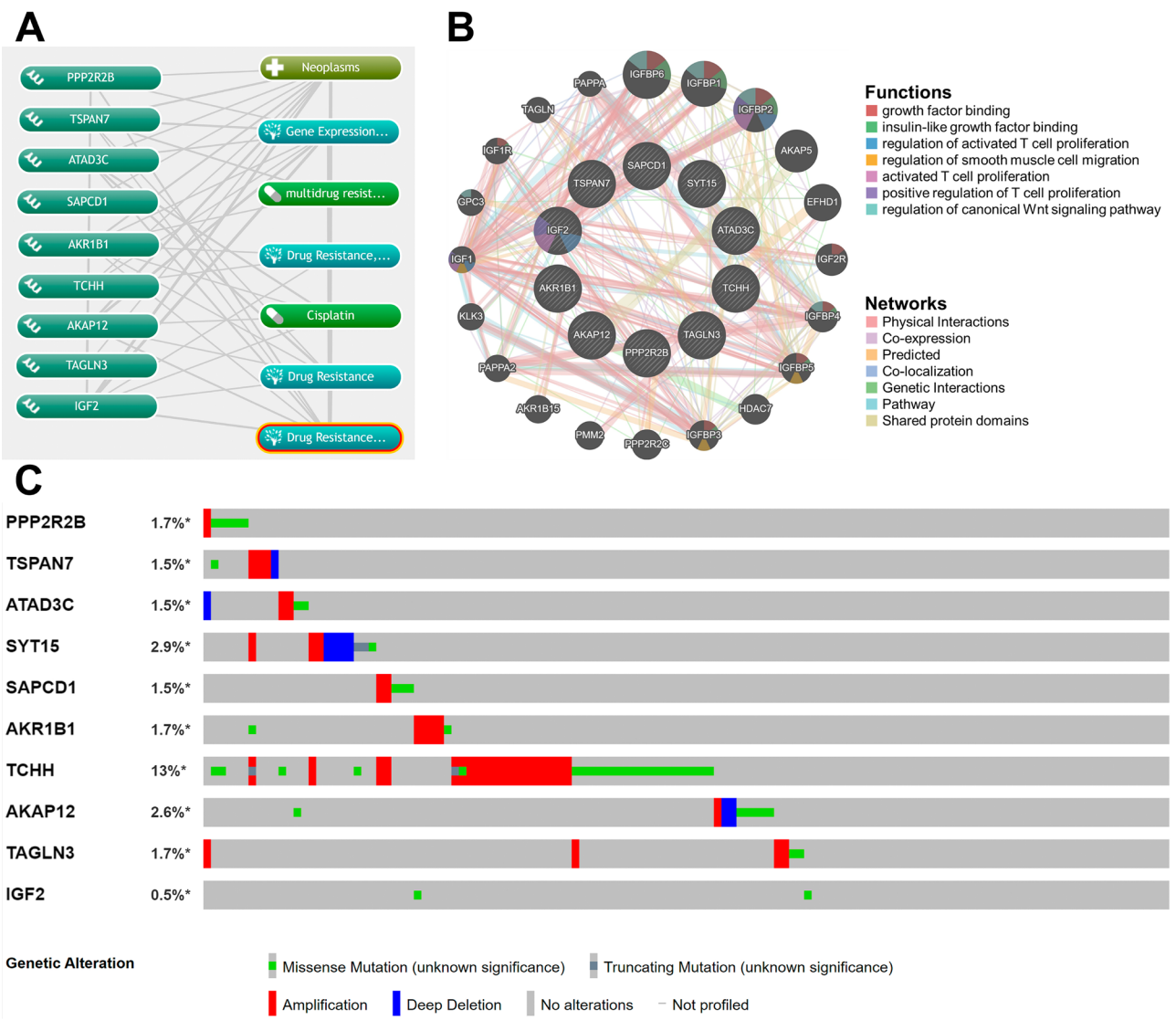


Figure S4. Expression levels of genes in bladder tumor and normal bladder tissues.

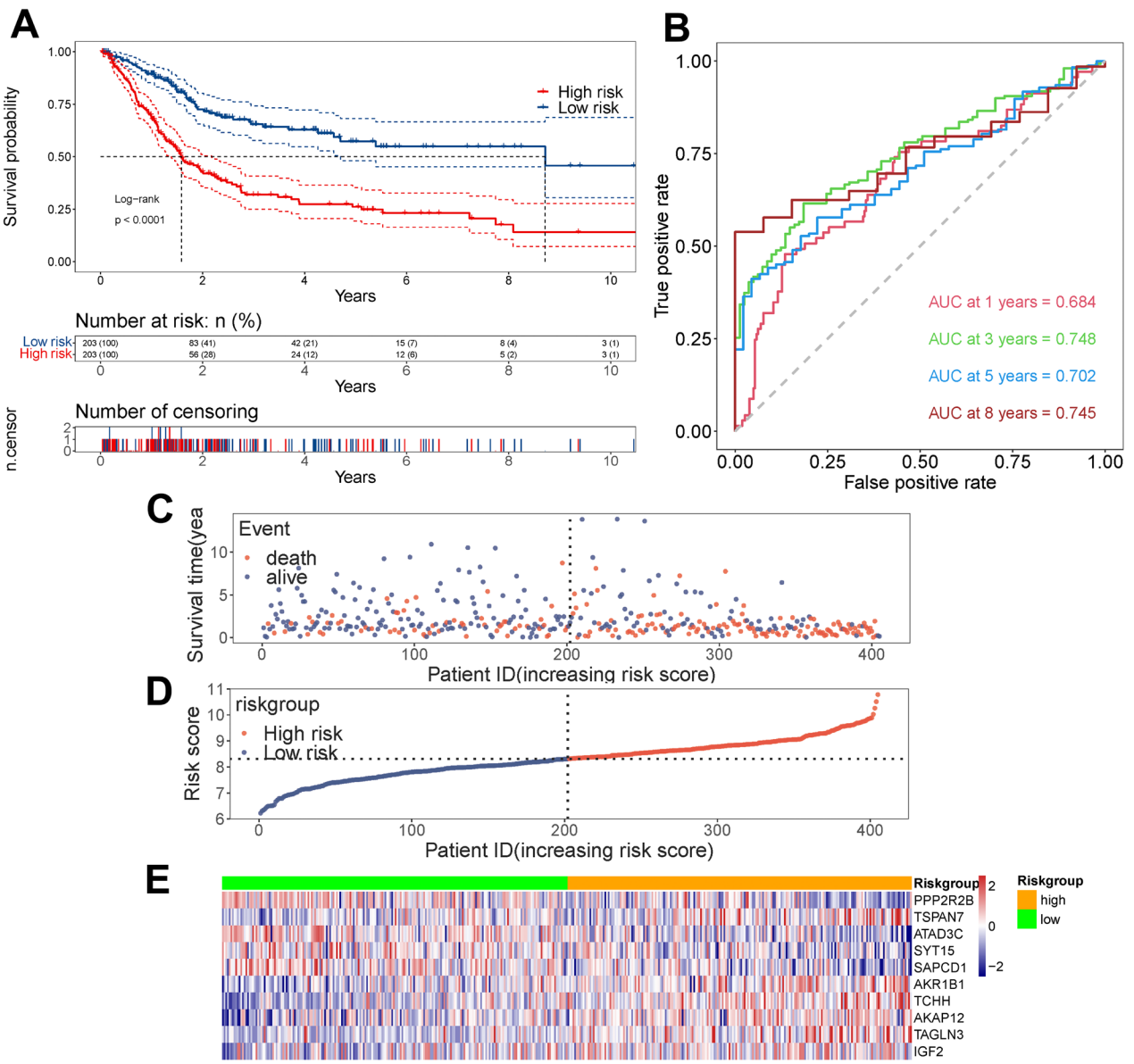
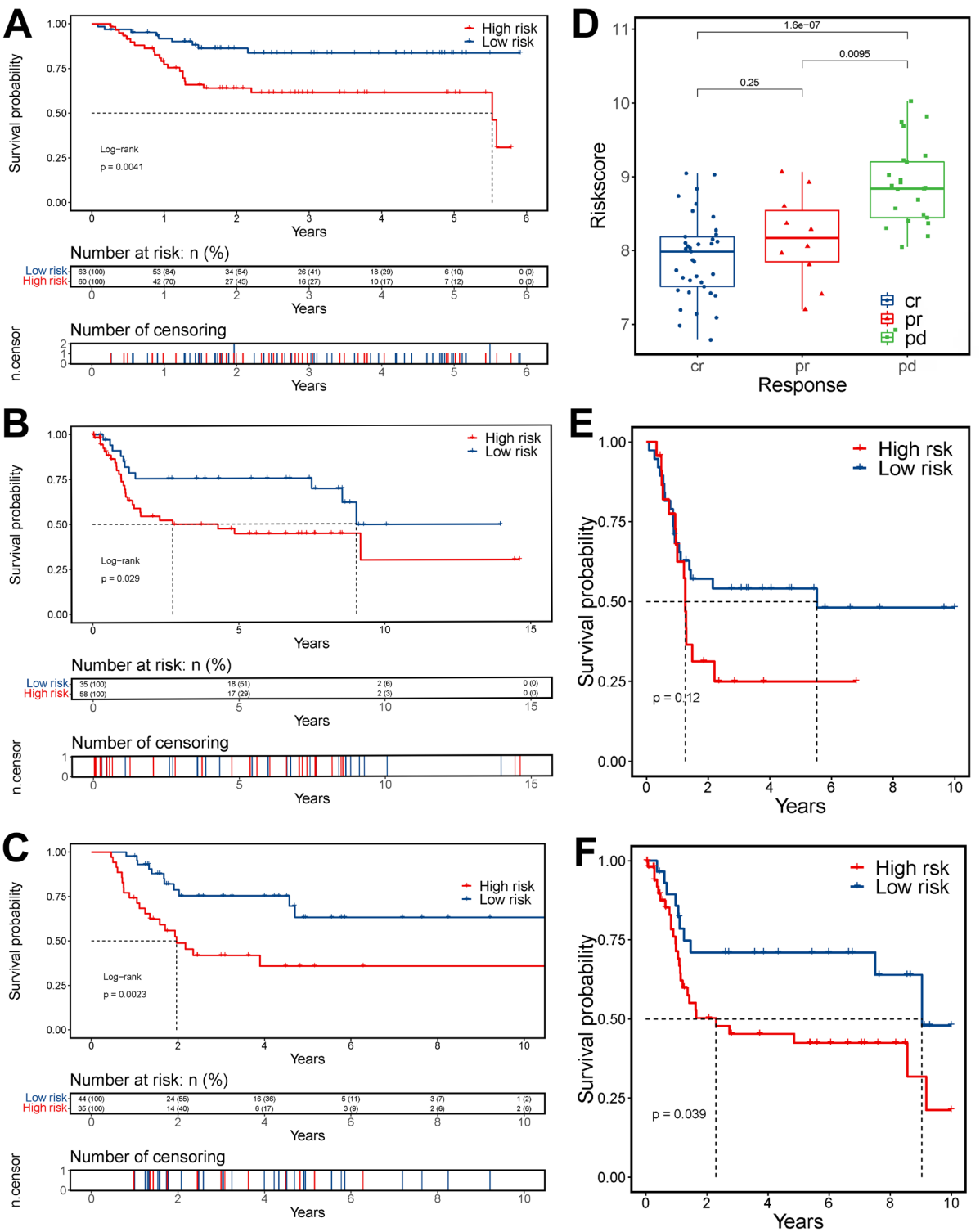
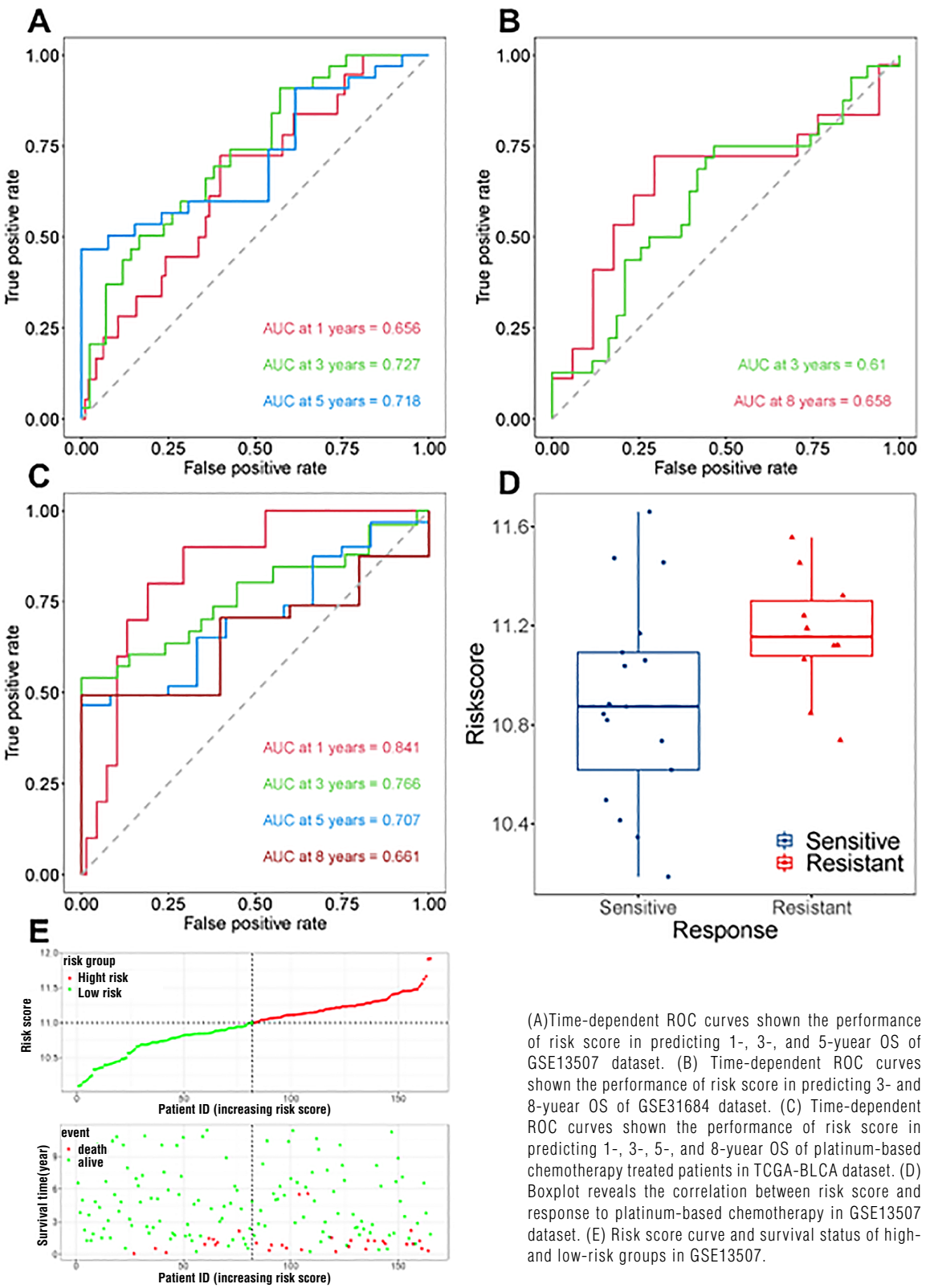


Figure S5. Subgroup analysis of risk group in training dataset.



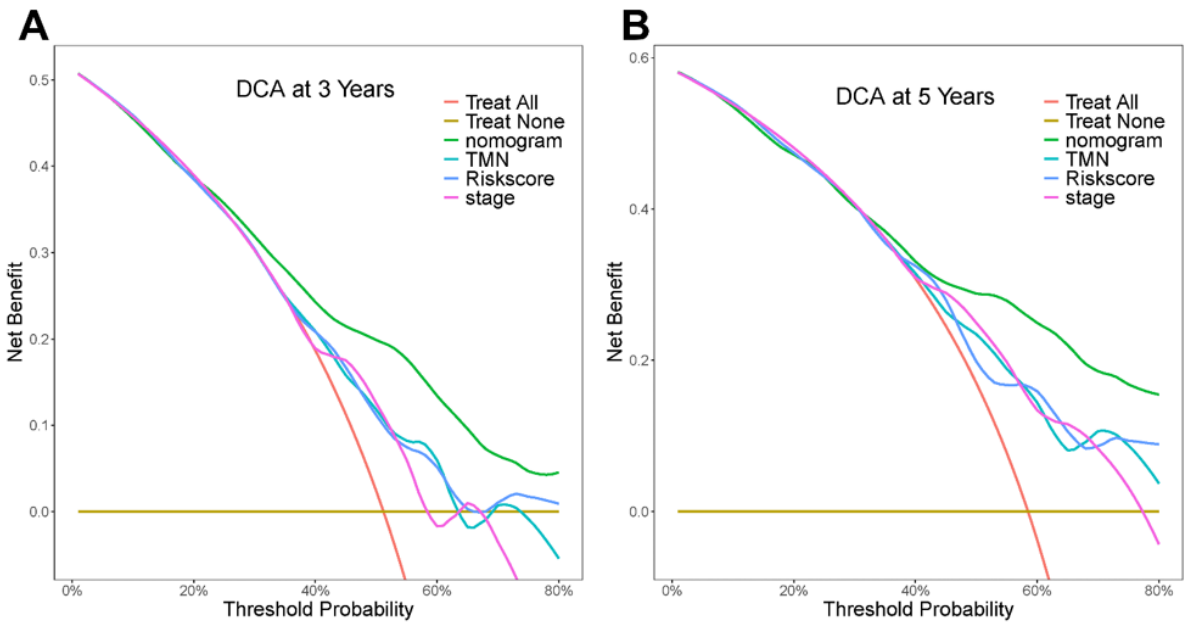
(A) Age < 68 year; (B) Age ≥ 68 year; (C) Female; (D) Male; (E) Subtype of papillary; (F) Subtype of non-papillary; (G) High grade; (H) Stage ii; (I) Stage iii; (J) Stage iii+iv; (K) Stage iv; (L) Pathologic stage of T2; (M) Pathologic stage of T3; (N) Pathologic stage of T3+T4; (O) Pathologic stage of T4; (P) Pathologic stage of M0; (Q) Pathologic stage of Mx; (R) Pathologic stage of N0; (S) Pathologic stage of N1+N2+N3.

Figure S6. Evaluating prognostic performance of gene-based model in validation group.



(A)Time-dependent ROC curves shown the performance of risk score in predicting 1-, 3-, and 5-yuear OS of GSE13507 dataset. (B) Time-dependent ROC curves shown the performance of risk score in predicting 3- and 8-yuear OS of GSE31684 dataset. (C) Time-dependent ROC curves shown the performance of risk score in predicting 1-, 3-, 5-, and 8-yuear OS of platinum-based chemotherapy treated patients in TCGA-BLCA dataset. (D) Boxplot reveals the correlation between risk score and response to platinum-based chemotherapy in GSE13507 dataset. (E) Risk score curve and survival status of high- and low-risk groups in GSE13507.

Figure S7. Estimation of nomogram.



Decision curves analysis (DCA) demonstrated the utility of nomogram in predicting 3-year (A) and 5-year (B) survival rate.

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One-day voiding diary in the evaluation of Lower Urinary Tract Symptoms in children

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ABSTRACT

Introduction: Voiding diary (VD) is an important tool in the evaluation of children with voiding symptoms. Voiding frequency, maximal voided volume (MVV), average voided volume (AVV) and nocturnal volume (NV) can be extracted and are valuable in diagnosing and monitoring these disorders. Recently, ICCS has reduced the period of data recording on VD from 3 to 2 days.We hypothesized that one day voiding diary would be enough for guiding treatment.

Materials and Methods: Children with overactive bladder (OAB) and primary monosymptomatic enuresis (PMNE) were oriented to fulfill a 3-day VD. Data obtained from VD were evaluated for the first day (1dVD), the first two days (2dVD), and all 3 days (3dVD) and compared according to the MVV, AVV, frequency, NV and expected bladder capacity (EBC). The Friedman, Student's t test and the Fisher's exact was used. ANOVA was used for multiple comparisons. We also used Pearson correlation test.

Results: Ninety-eight children were included, 59 had PMNE and 30 OAB. Frequency, AVV and VN were similar regardless how many days the voiding episodes were recorded. Only MVV was higher by a mean of only 32 mL on 3dVD compared to 1dVD. A 1dVD has a sensitivity of 93,9% and a positive likelihood ratio of 2.2. As for the correlation of MVV and EBC it was observed that in 83% of children, MVV was lower than EBC. MVV corresponds to 67% and 69% of EBC in children with PMNE and OAB, respectively.

Conclusion: We believe that 1dVD is sufficient to assess these children. It has a high sensitivity and good correlation to 3dVD in evaluating these children. Bladder capacity in this population, evaluated by maximum voided volume, was close to 68% of that obtained by the EBC.

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INTRODUCTION

Lower urinary tract dysfunctions (LUTD) are disorders that can occur during the storage and voiding phases of micturition in the absence of neurological disease or lower urinary tract obstruction (1). Overactive bladder (OAB) is the most common type, being one of the most prevalent urinary disorders in childhood and defined as a condition that affects children presenting urinary urgency with or without incontinence and may or may not be associated with frequency (2).

Primary monosymptomatic nocturnal enuresis (PMNE) is characterized by involuntary voiding during sleep and is another prevalent disorder in childhood, affecting about 10 to 15% of children aged five to six years and is also included in the group of LUTD. OAB and PMNE are frequently associated with emotional and behavioral problems in children and directly affects their quality of life and many are still at high risk of suffering some type of punishment and can cause impacts on family members who live with the child (3-6). Therefore, clinical diagnosis and safe management of such disorders are of great importance, as well as instituting and monitoring the most appropriate treatment in order to minimize the short- and long-term consequences (7).

Voiding diary (VD) is an extremely useful tool that allows to draw a profile of the urinary routine, determining characteristics of bladder function in adults and children and is characterized by being a simple, non-invasive, low-cost method, free from complications, which best reproduces voiding habits (8, 9). Important measures such as voiding frequency, maximal voided volume (MVV), average voided volume (AVV) and nocturnal volume (NV) are easily extracted from VD and are valuable in diagnosing and monitoring these diseases (1, 2). According to the International Children Continence Society (ICCS), VD is one of the three diagnosis tests included in the so called non-invasive urodynamics, that also includes ultrasound with the evaluation of post-voided residual and uroflowmetry (1). The same study, ICCS has reduced the period of data recording on VD from 3 to 2 days. Our hypothesis is that one day voiding diary is enough for guiding treatment.

Studies in adult women have shown a strong correlation between the MVV obtained from a VD and the volume obtained when a strong voiding desire was referred during an urodynamics test, reinforcing the importance of the VD as a non-invasive alternative to urodynamics (10). Although VD is being reported in most of recent studies on LUTD, the analysis of the data obtained from it has shown great unconformities. Although VD is being reported in most of recent studies on LUTD, the analysis of the data obtained from it has shown great unconformities. Parents often complain of the difficulty of collecting all voiding episodes, drinking and bowel movements data for three, or even, two days as previously proposed (1, 11).

Therefore, the aim of the present study is to evaluate whether recording data in a VD for only one day would be enough to guide treatment, and also to evaluate and compare the maximum voided capacity to the expected bladder capacity (EBC) calculated by the formula proposed by Koff et al. (12).

MATERIALS AND METHODS

A cross-sectional observational study was carried out in our LUTD clinic. The sample consisted of children aged 5 to 14 years presenting with OAB and PMNE who were instructed to fulfill a three-day VD as part of their assessment.

Parents and children were instructed on the objectives and methods of the study and after agreeing with them, they were invited to sign the informed consent and assent. The study was approved by the institution ethics committee under the number 1796620 and registered in the RBR-3w2mxmw.

The data obtained from the VD were evaluated on the first day (1dVD), the first two days (2dVD) and all 3 days (3dVD) and compared according to the MVV, AVV, voiding frequency and NV, which includes night volume, measured by asking the parents to put a diaper in their children for the night and weighting it in the morning, added to the volume of the first morning void.

Children and adolescents with kidney, neurological and psychiatric diseases, secondary noc-

turnal enuresis, as well as conditions associated with LUTD such as diabetes or use of diuretic medications, and those whose parents did not agree to participate in the study, did not fill out correctly the VD, or did not perform any of the requested tests were not included in the study.

Before being included in the study, parents and children answered a structured questionnaire as well as the DVSS score (13), including daytime and nighttime questions on voiding function and habits, and were submitted to clinical evaluation. A kidney and bladder ultrasound were done to evaluate the urinary tract and post-voided residual and a uroflowmetry was done to evaluate voiding pattern. Those with high post-voided residual on ultrasound or an interrupted or staccato curve on uroflowmetry were not included in the study. The urotherapist nursing staff oriented on how to fulfill the 3 days VD and a dry night diary for 14 consecutive nights.

After the child returned with the VD and test results, those who fulfilled inclusion criteria were included in the study. Data from VD were analyzed by the urotherapist nurse. MVV was considered the highest voided volume excluding first morning void. Average voided volume was the average of all voiding, also excluding first morning voids. Voiding frequency was the mean frequency during the analyzed period and nocturnal volume was calculated adding the first morning void to the weight of the diaper. The formula adopted to calculating EBC used in this study was that proposed by Koff and suggested by ICCS (EBC= [age (yrs)+1] ×30 mL) (1, 12).

Quantitative data was expressed as mean ± standard deviation (SD) while qualitative variables were expressed as absolute values, percentages, or proportions. The Friedman or Student's t test were used to compare continuous variables, and the Fisher's exact or chi-square test was used for categorical comparisons. All tests were 2-sided with $p < 0.05$ considered statistically significant. ANOVA was used for multiple comparisons. We also used Pearson correlation test to correlate 1dVD to 3dVD. Considering 3dVD as a reference test, sensitivity, specificity, overall accuracy, and predictive values, are described to 2dVD and 1dVD on estimates of low MVV. Analysis was performed using commercially available statistical software (GraphPad Prism, version 8.03 for Windows, San Diego California USA).

RESULTS

A total of 98 children aged 8.23 ± 2.26 years (53% male) were included. Of these, 59 had PMNE with a mean age of 8.58 ± 2.35 years of age, being 30 boys (50.84%) and 39 presented OAB with a mean age of 7.72 ± 2.05 years old being 22 boys (56.41%).

Frequency, AVV, and NV were similar, regardless of how many days VD was recorded (Table-1). The mean of difference for MVV was 19.8 mL higher in 2dVD compared to 1dVD ($p<0.001$) and 12.6 mL higher in 3dVD compared to 2dVD ($p<0.001$). Comparing 3dVD to 1dVD, it was 32.1 mL higher ($p <0.01$) (Table-1 and Figure-1). Pearson test showed a good correlation for MVV

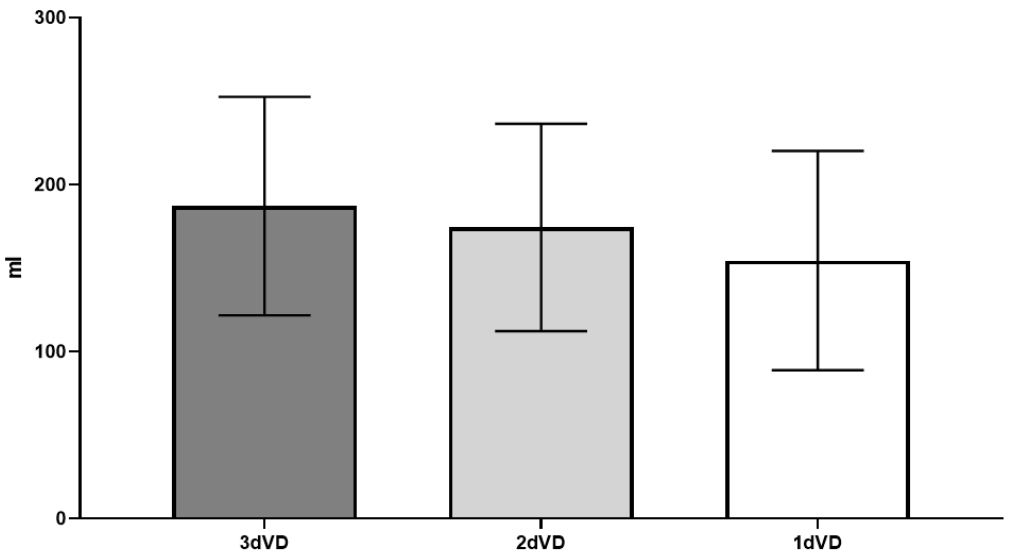
Table 1 - Comparison of voiding frequency, MVV, AVV and NV in the 3dVD, 2dVD and 1dVD calculations of the VD.

Voiding Diary (number of days) vs. Voiding Parameters (Mean ? SD)				
	3dVD	2dVD	1dVD	p-value*
Frequency (voids/day)	6.6 ± 2.3	6.6 ± 2.2	6.8 ± 2.5	0.960
MVV (mL)	184.8 ± 65.9	172.2 ± 62.6	152.7 ± 65.3	0.0001
AVV (mL)	103.5 ± 39.2	104.5 ± 46.2	102.9 ± 46.9	0.133
NV (mL)	269.0 ± 148.0	290.5 ± 128.5	275.3 ± 121.9	0.356

***p value was < 0.001 when paring all groups for MVV (3dVD vs. 2dVD, 3dVD vs. 1dVD, and 2dVD vs. 1dVD)**

MVV = Maximum Voided Volume; AVV = Average Voided Volume; NV = Nocturnal Volume; 3dVD = Three days Voiding Diary; 2dVD = Two days Voiding Diary; 1dVD = One day Voiding Diary; SD = Standard Deviation

Figure 1 - Comparison between Mean Maximum voided volume (MVV) obtained from 3 days (3dVD), 2 days (2dVD) and 1day (1dVD) voiding diary.

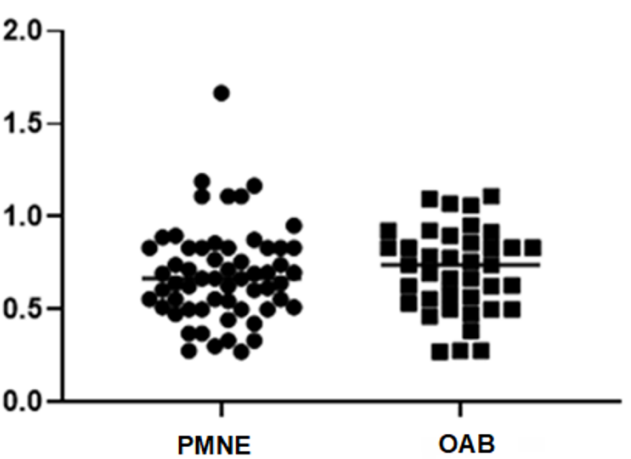


between 1dVD and 3dVD (r=0.82; CI: 0.74-0.87; p<0.001).

A discrepancy was observed between MVV and EBC in both groups. For the PMNE group the mean EBC was 287.29 ± 70.51 mL while the mean MVV was 191.02 ± 67.41 mL obtained on the 3dVD, 173.98 ± 63.99 mL for 2dVD, and 165.51 ± 67.20 mL for 1dVD. MVV corresponded to 67% of EBC when a 3-day VD was collected, 61% for 2dVD, and 58% for 1dVD. Similarly, in the OAB group, the mean EBC was 263.08 ± 61.74 mL and MVV was 181.41 ± 62.65 mL for 3dVD, 175.00 ± 60.01 mL for 2dVD, and 138.00 ± 60.34 mL for 1d VD, which corresponded to 69%, 67%, and 53% of EBC for one, two-, and three-days voiding diary, respectively. Considering only the 3dVD the maximum voided volume obtained was 67% of EBC for PMNE children and 69% of EBC for OAB children (Figure-2).

Considering 3dVD as the reference test to identify lower bladder capacity, especially that bellow 65% of EBC, (1) 1dVD has sensitivity of 93.87% (83.13 to 96.72%), specificity of 57.14% (42.21% to 71.18%), and an overall accuracy of 75.5% (65.8% to 83.6%, CI 95%). The positive and negative predictive values are 68.66% (61.14% to 75.31%) and 90.32% (75.23% to 96.63%), respectively.

Figure 2 - Ratio between Maximum Voided Volume (MVV) obtained for 3 days voiding diary and Expected Bladder Capacity (EBC). Observed was 67% of EBC for PMNE children and 69% of EBC for OAB children.



If the data is collected for two consecutive days the sensitivity increases to 97.96% (89.15% to 99.95%), specificity to 87.75% (75.23% to 95.37%), and the overall accuracy to 92.9% (85.8% to 97.1%, CI 95%). The positive and negative predictive values are 88.89% (79.06% to 94.43%) and 97.73% (86.04% to 99.67%).

DISCUSSION

Objective measurements of lower urinary tract symptoms are a clinical challenge. Although VD is routinely used in clinical practice for the primary assessment of children and adults, there are few studies on the use of VD in children.

The present study demonstrates that the number of days on which VD is performed, whether 1, 2 or 3 days, does not influence the analysis of voiding frequency, AVV and NV. In the other hand, MVV was lower when VD was collected for only one day, this difference represents 19.5 mL in comparison to 2dVD, which is the proposed number of days for VD by ICCS, a value we do not consider to be clinically significant. This is reinforced when, in the comparison between 2dVD and 3dVD values only a 12.6 mL difference was observed. Comparing 3dVD to 1dVD the difference found was also small (32.1 mL) and has a good correlation (r=0.82). In the authors opinion, this difference of a small volume (32.1 mL) in not clinically significant to the point of interfering in the diagnosis or treatment of these children and, to reinforce this statement, AVV was similar in all three groups (3dVD: 103.5 ± 39.2, 2dVD: 104.5 ± 46.2, and 1dVD 102.9 ± 46.9).

Different studies on the amount of days VD should be collected have suggested that 3 days are enough and trustable (14, 15). Although Homma et al. (16) ensure that longer periods can be more representative and with less data variation, Brown et al. (14) state that the length of the test period impairs patient compliance. Therefore, shorter periods of data collection on VD would be less burdensome and has less impact on the patient, tending to be more precise and reliable. Groutz et al. found that compliance decreased about 76% when VD was increased by 72 hours, while in a 24-hour diary, compliance was 92% (17).

Even with the latest revision and guidance from the ICCS (1), which reassures that performing the VD for 2 non-consecutive days is satisfactory, there are few studies in the literature that analyze the best period to evaluate the child's voiding pattern using the VD. Lopes et al. (11) assessed that the 2dVD is statistically and clinically comparable to a 3dVD and concluded that 2 days is a sufficient period to assess bladder capacity and liquid intake in children.

In our clinical experience, even after carefully explaining the importance and how to collect VD data by an experienced team of urotherapists, we have witnessed numerous complaints regarding the obstacles that hinder the dynamics of performing and filling it out. Lack of time, availability of an adult to assist with fulfilling it are the most reported complains. In addition, completing it for 3 consecutive days takes at least one school day for the child and a workday for the adult, even if including the weekend.

Mazurick and Landis (18) comparing 3 consecutive days of VD to one single day in women with interstitial cystitis, demonstrate that the measurements of VD during the week were not significantly different from those on weekends and also ensure that the VD can be reduced to a single day. Therefore, even with the differences in MVV volume found in the present study, we believe that only 1-day VD is sufficient for an adequate diagnostic evaluation and treatment guidance, especially for those low compliant families.

Because VD is a new event in the child's routine, as well as the child being enchanted by the idea of "peeing in the cup" and having more attention from parents, clinical impressions is that these changes could fantasize a higher frequency of voiding on the first day of VD, which was not true, being the frequency average similar between 1dVD, 2dVD, and 3dVD. The same was found by Lopes et al. (11), which showed that even with a higher average number in 2dVD, the voiding frequency agreed in 83.4% of cases with the 3dVD. Kwak et al. (19) also evaluated the 3-day diaries and questionnaire data of children with mono and non-monosymptomatic nocturnal enuresis and did not notice statistical differences in relation to the number of voiding.

Bladder capacity is an important parameter for assessing the lower urinary tract. Whether in the adult or pediatric population, studies have shown that VD has advantages over other methods, as it reveals the voiding routine more reliably (20, 21).

Researchers have suggested that bladder capacity is described as a factor involved in the etiology of PMNE, since children with enuresis

have a relative decrease in EBC when compared to non-enuresis children (22, 23). As for the analysis of the relationship between MVV and EBC the present data demonstrate that 82.7% of the evaluated children have a MVV lower than the EBC. In our sample we have observed that MVV obtained by the VD was 67% of EBC in children presenting PMNE and 69% in those with OAB.

In opposite to the finds showed herein, Uluocak et al. (21), when comparing uroflowmetry with maximum cystometric capacity and MVV regarding the EBC in 84 children with OAB, realized that there is no significant difference between them and states that the VD was a reliable and non-invasive method for this group of patients.

Martinez-Garcia et al. (24) reviewing children's normal bladder capacity and measuring children's maximum normal voiding volumes and still comparing them with the usual formulas, concluded that the most accurate reference model for obtaining the MVV was based on records of VD and that even the simple linear formulas of Koff or Rittig are imprecise to be used in clinical situations. Following these findings, the present study also demonstrates that the formula suggested by ICCS to be used (1) is not precise in estimating bladder capacity in children with OAB and PMNE and both disorders have similar association between MVV and EBC, being MVV about 68% of EBC.

According to our findings, both 1dVD and 2dVD have a good sensitivity in evaluating MVV in children with PMNE and OAB, missing only a few individuals with very low bladder capacity (< 65% of EBC). In the other hand, doing only one-day VD has a lower specificity, which means that it includes a greater number of false positive individuals (those with lower capacity in 1dVD and normal capacity when evaluated with a 3dVD).

Although several measures were taken in order to avoid problems in data collection in the present study, such as team training on daily orientation, strict inclusion criteria, and patient evaluation, some weaknesses must be highlighted, such as the sample size and the non-standardization of measuring cups, as well as diaper weighting scales. In addition, the loss of incomplete diaries after the first meeting was not evaluated, since one of the inclusion requirements was the correct completion of the VD.

CONCLUSIONS

Although MVV was lower by a small volume in 1dVD, we believe that 1-day VD is adequate to assess PMNE and OAB children, especially for those low compliant families. It shows high sensitivity and can provide a good snapshot of children's voiding habits. Bladder capacity in this population, evaluated by maximum voided volume is 67% and 69% of that obtained by the EBC formula proposed by ICCS for enuresis and OAB children, respectively.

FUNDING INFORMATION

The present study received financial support from the Fundação de Amparo a Pesquisa do Estado de Minas Gerais (FAPEMIG)

COMPLIANCE WITH ETHICAL STANDARDS

The study was approved by the institution ethics committee under the number 1796620

Parents and children were instructed on the objectives and methods of the study and after agreeing with them, they were invited to sign the informed consent and assent. All included subjects have signed the informed consent.

The study was registered in the ReBEC (Registro Brasileiro de Ensaios Clínicos) under the number RBR-3w2mxmw.

The data that support the findings of this study are available from the corresponding author. Data will be made available upon request.

ACKNOWLEDGMENTS

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CONFLICT OF INTEREST

Only the corresponding author (José Murillo B. Netto) has a conflict of interest to declare,

which is the Fundação de Amparo a Pesquisa do Estado de Minas Gerais (FAPEMIG).

All other authors have no disclosure.

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The geriatric nutritional risk index predicts complications after nephrectomy for renal cancer

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ABSTRACT

Purpose: We examined if malnutrition, as defined by the Geriatric Nutritional Risk Index (GNRI), is independently associated with 30-day postoperative complications in patients undergoing nephrectomy for the treatment of renal cancer.

Materials and methods: Using the American College of Surgeons National Surgical Quality Improvement Program database from 2006-2019, we identified patients ≥65 years old who underwent nephrectomy for renal cancer. The following formula for GNRI was used to define preoperative nutritional status: 1.489 x serum albumin (g/L) + 41.7 x (current body weight [kg]/ ideal body weight [kg]). Based on the GNRI, patients were classified as having no (> 98), moderate (92-98), or severe malnutrition (< 92). After adjusting for potential confounders, multivariable logistic regression analyses were performed to assess the association between GNRI and 30-day postoperative complications. Odds ratios (OR) with 95% confidence intervals (CI) were reported.

Results: A total of 7,683 patients were identified, of which 1,241 (16.2%) and 872 (11.3%) had moderate and severe malnutrition, respectively. Compared to normal nutrition, moderate and severe malnutrition were significantly associated with a greater odds of superficial surgical site infection, progressive renal insufficiency, readmission, extended length of stay, and non-home discharge. Severe malnutrition was also associated with urinary tract infection (OR 2.10, 95% CI 1.31-3.35) and septic shock (OR 2.93, 95% CI 1.21-7.07).

Conclusion: Malnutrition, as defined by a GNRI ≤ 98, is an independent predictor of 30-day complications following nephrectomy. The GNRI could be used to counsel elderly patients with renal cancer prior to nephrectomy.

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INTRODUCTION

In 2020, more than 430,000 people were diagnosed with renal cancer and approximately 180,000 people died from this disease worldwide (1). The incidence of kidney cancer is strongly related to age. Approximately 50% of new diagnoses are in elderly patients (≥ 65 years of age) (2). Nephrectomy remains the gold standard treatment in most cases (3). Overall complication rates for nephrectomy range between 10 and 30% depending on the surgical approach and extent (4).

Perioperative malnutrition is a known independent predictor of poor postoperative outcomes in general surgery, especially among the elderly (5). Malnutrition can be as high as 70% in elderly oncology patients (6-8). Screening tools

can aid in identifying nutritional status among older patients undergoing oncological surgery, but the abundance of questionnaires and calculators has impeded widespread implementation of perioperative nutritional assessment in clinical practice (5, 9, 10).

Among the many tools available to assess preoperative nutritional status in the elderly, the Geriatric Nutritional Risk Index (GNRI) is simple to calculate, as it utilizes changes in height and weight, in addition to serum albumin (11). While the GNRI was first developed for predicting nutrition-related risk of morbidity and mortality among hospitalized geriatric patients, it has also been found to be an independent predictor of outcomes among elderly patients with cancer (11-13). In renal cancer, the GNRI has been shown to be an independent predictor of overall, cancer-specific, and recurrence-free survival (14, 15). However, the role of GNRI in predicting short-term outcomes after nephrectomy has not been thoroughly evaluated (16). We postulated that malnutrition, as defined by GNRI, may be independently associated with worse 30-day outcomes following nephrectomy for renal cancer. To test this hypothesis, we performed a retrospective cohort study of patients undergoing nephrectomy for renal cancer, evaluating the association between GNRI and 30-day postoperative outcomes.

MATERIALS AND METHODS

Study design

After receiving exempt status from our Institutional Review Board (#202101589), we queried the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) database. Using data from 2006 to 2019, we identified patients ≥ 65 years old with a diagnosis of renal cancer (International Coding of Diseases, Ninth Revision [ICD-9] codes 189.x and ICD-10 codes C64.x) undergoing radical (Current Procedural Terminology [CPT] codes 50220, 50225, 50230, 50545, 50546) and partial nephrectomy (CPT codes 50240 and 50543). To account for the half-life of albumin, only patients who had serum albumin levels measured within 30 days prior to surgery were included. Patients with an American Society of Anesthesiologists (ASA) classification score of 5, ascites, preoperative sepsis, or ventilator dependence at the time of surgery were excluded. We also excluded emergency cases and patients with missing data, except for patients with missing race or ethnicity data.

Variables

Patient preoperative profiles included age, sex, body mass index (BMI), functional status, ASA classification, 5-item modified frailty index (5i-mFI), smoking status, comorbidities (diabetes mellitus [DM], hypertension [HT], congestive heart failure [CHF], severe chronic obstructive pulmonary disease [COPD], dyspnea, disseminated cancer, > 10% body weight loss in the 6 months preceding surgery, chronic steroid use, bleeding disorder, preoperative dialysis, acute renal failure), and preoperative laboratory values (serum creatinine, hematocrit, white blood cell count, and platelet count). All preoperative laboratory values included were measured within 30 days prior to surgery. According to NSQIP, bleeding disorder is defined as "increased risk of bleeding due to an underlying hematological disorder or chronic anticoagulation" (17). Operative data included nephrectomy extent (partial or radical), surgical approach (open or minimally invasive [MI]), wound classification (I – clean, II clean/contaminated, III – contaminated, IV – dirty/infected), and operative time. CPT codes 50220, 50225, 50230, and 50240 were classified as open while CPT codes 50545, 50546, and 50543 were classified as MI. ASA classification was dichotomized into two categories: ≤ Class 2 and > Class 2. The 5i-mFI has been observed to predict postoperative complications following urologic surgery (18, 19). It is calculated based on the presence of the following: DM, HT requiring medication, CHF, respiratory disease (COPD or pneumonia), and partial/total dependence prior to surgery (20).

Nutritional Assessment

According to previously published literature, malnutrition was defined based on BMI < 18.5 kg/m^2, serum albumin < 3.5 g/dL, and > 10% body weight loss in the last 6 months (5). Nutritional status according to the GNRI was calculated using

the following variables: weight, height, and preoperative serum albumin. GNRI was calculated as: (1.489 x serum albumin [g/L]) + (41.7 x [current body weight (CBW)/ ideal body weight (IBW)]) (11). IBW was calculated as: (height x height) x 22, and it was capped at 1 if it exceeded the CBW (11, 21). Following a similar classification to that used by Bouillane et al., we categorized patients into three groups: severe malnutrition (GNRI < 92), moderate malnutrition (GNRI 92 - 98), and normal nutritional status (GNRI > 98) (11).

Endpoints

The primary outcome was rate of any NSQIP complication, defined as: cardiac arrest requiring cardiopulmonary resuscitation, myocardial infarction, death, pneumonia, unplanned intubation, failure to wean from ventilator, pulmonary embolism (PE), deep venous thrombosis (DVT) requiring therapy, stroke, intraoperative or postoperative transfusion, sepsis or septic shock, acute renal failure, progressive renal insufficiency, urinary tract infection (UTI), wound dehiscence, or surgical site infection (SSI) [superficial, deep incisional, or organ/space]. Secondary endpoints were: major complications (defined as Clavien-Dindo [CD] III and IV), extended length of stay (LOS), readmission, reoperation, and non-home discharge (22).

Major complications included cardiac arrest requiring cardiopulmonary resuscitation, myocardial infarction, unplanned intubation, failure to wean from ventilator, PE, stroke, sepsis or septic shock, acute renal failure, deep incisional SSI, and organ/space SSI. Extended LOS was defined as hospital stay > 75th percentile (partial nephrectomy > 4 days and radical nephrectomy > 6 days). Non-home discharge was defined as any discharge destination that was not 'home' or 'facility which was home'. Complications were also reported and analyzed individually.

Statistical analysis

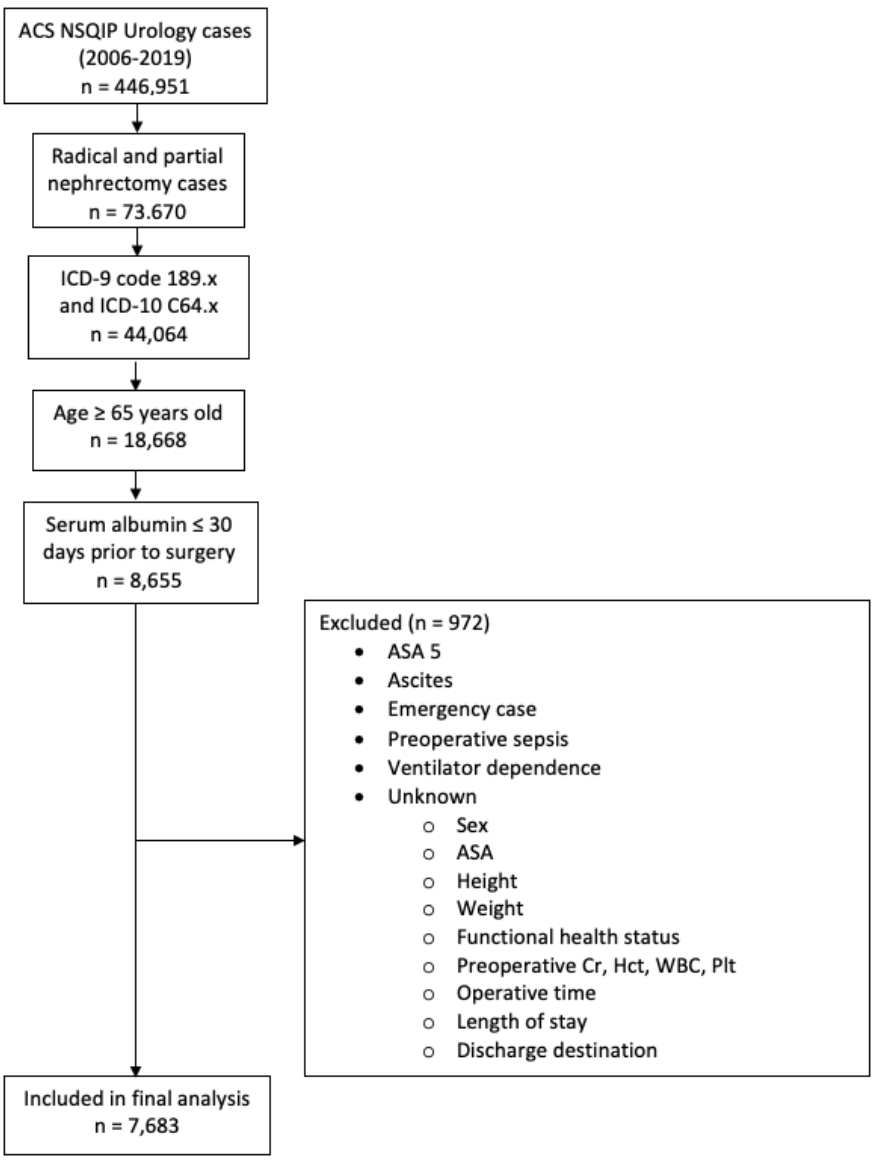
Categorical variables were reported as frequencies (%) while continuous variables were reported as median with interquartile range (IQR). Chi-square and Kruskal-Wallis tests were used where appropriate for categorical and continuous variables. Multivariable logistic regression analyses (MLRA) were used to determine if GNRI was an independent predictor of 30-day complications following nephrectomy. Besides GNRI, the other confounders used in the models were age (continuous), sex (male vs. female), race (Caucasian vs. African American, Other, or Unknown), ASA classification (< 2 vs. ≥ 3), BMI (continuous), 5i-mFI (0 vs. 1, 2, or ≥ 3), bleeding disorder (no vs. yes), dyspnea (no vs. yes), steroid/immunosuppressant for a chronic condition (no vs. yes), smoker (no vs. yes), disseminated cancer (no vs. yes); preoperative blood transfusion (no vs. yes), acute renal failure (no vs. yes), dialysis requirement (no vs. yes), hematocrit (continuous), creatinine (continuous), hematocrit (continuous), white blood cell count (continuous), platelet count (continuous), nephrectomy type (radical vs. partial), surgical approach (open vs. MI), wound classification (I vs. II, or III, or IV), and operative time (continuous).

Two sets of MLRA models were executed: one with GNRI as a categorical variable (GNRI > 98 as the reference group vs. GNRI 92 - 98 or GNRI < 92), and the other one with GNRI as a decreasing continuous variable. Results of the analyses were reported as odds ratios (OR) with their corresponding 95% confidence intervals (95% CI). The variance inflation factor (VIF) was examined to check for multicollinearity among the models. Variables with a VIF ≥ 2.5 were considered significantly multicollinear and were eliminated from the models. Because patients with disseminated cancer were included in the original cohort, we performed a sensitivity analysis without patients undergoing cytoreductive nephrectomy to investigate whether statistically significant differences could be attributed to metastatic disease. All statistical analyses were performed using the EZR plugin for R (23). Statistical significance was set at p-value < 0.05, and all tests were two-tailed.

RESULTS

A total of 7,683 cases met the inclusion criteria with 241 (16.2%) and 872 (11.3%) identified as having moderate (GNRI 92 - 98) or severe malnutrition (GNRI < 92) respectively (Figure-1).

Figure 1 - Flowchart for patient selection.



The demographic and operative profiles of all patients were summarized (Table-1). The number of patients meeting the definition of malnutrition according to BMI (< 18.5 kg/m²) and serum albumin (< 3.5 g/dL) was 58 (0.7%) and 1,039 (13.2%), respectively. Additionally, 184 (2.3%) patients were classified as having lost more than 10% of their body weight within 6 months prior to surgery. Overall, patients with a BMI < 18.5 kg/m², serum albumin < 3.5 g/dL, and > 10% body weight loss had significantly lower GNRI scores compared to their counterparts (Figure-2).

Comparisons of unadjusted 30-day outcomes following nephrectomy among the three study groups were performed (Table-2). Thirty-day outcomes were generally worse for the moderate and severe malnutrition groups compared to patients with a normal nutritional status. The unadjusted 30-day postoperative complication rates were significantly worsened as the severity of malnutrition increased. Overall, malnourished patients (GNRI ≤ 98) had higher rates of a complication compared to patients with a normal nutritional status (GNRI > 98). Likewise, rates of 30-day mortality and ma-

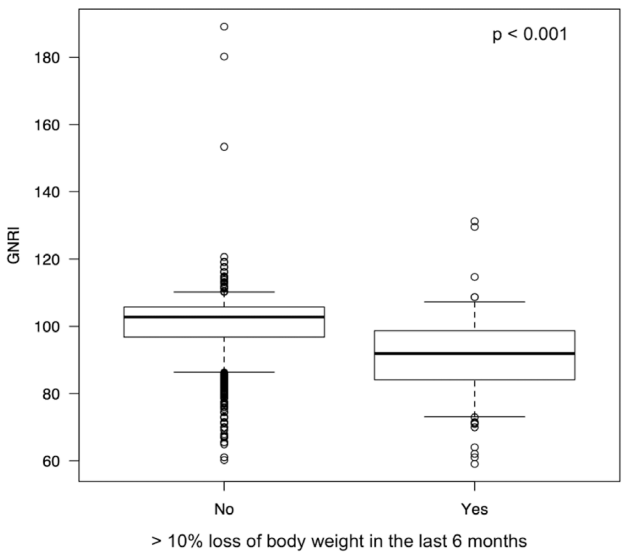
Table 1 - Patient Demographics and Surgical Procedure Characteristics.

Variables	All patients (n=7863)	GNRI <92 (n=872)	GNRI 92-98 (n=1241)	GNRI >98 (n=5750)
Sex				
Male	4948 (62.9%)	511 (58.6%)	754 (60.8%)	3683 (64.1%)
Female	2915 (37.1%)	361 (41.4%)	487 (39.2%)	2067 (35.9%)
Race				
Caucasian	6233 (79.3%)	672 (77.1%)	952 (76.7%)	4609 (80.2%)
African American	609 (7.7%)	81 (9.3%)	118 (9.5%)	410 (7.1%)
Other	264 (3.4%)	35 (4.0%)	37 (3.0%)	192 (3.3%)
Unknown	757 (9.6%)	84 (9.6%)	134 (10.8%)	539 (9.4%)
Hispanic ethnicity				
Yes	437 (5.6%)	48 (5.5%)	69 (5.6%)	320 (5.6%)
No	6730 (85.6%)	721 (82.7%)	1051 (84.7%)	4958 (86.2%)
Unknown	696 (8.9%)	103 (11.8%)	121 (9.8%)	472 (8.2%)
Age (years)	71.00 [68.00 - 76.00]	72.00 [68.00 - 77.00]	72.00 [68.00 - 77.00]	71.00 [67.00 - 75.00]
BMI (kg/m²)	29.01 [25.69 - 33.17]	27.08 [23.51 - 32.14]	28.89 [25.11 - 33.73]	29.25 [26.11 - 33.20]
Weight loss (%)	184 (2.3%)	92 (10.6%)	38 (3.1%)	54 (0.9%)
ASA				
≤2	1934 (24.6%)	128 (14.7%)	230 (18.5%)	1576 (27.4%)
>2	5929 (75.4%)	744 (85.3%)	1011 (81.5%)	4174 (72.6%)
Functional Status				
Independent	7715 (98.1%)	819 (93.9%)	1204 (97.0%)	5692 (99.0%)
Dependent	148 (1.9%)	53 (6.1%)	37 (3.0%)	58 (1.0%)
5i-MFI				
0	1471 (18.7%)	171 (19.6%)	219 (17.6%)	1081 (18.8%)
1	4091 (52.0%)	406 (46.6%)	628 (50.6%)	3057 (53.2%)
2	2090 (26.6%)	243 (27.9%)	355 (28.6%)	1492 (25.9%)
≥3	211 (2.7%)	52 (6.0%)	39 (3.1%)	120 (2.1%)
Current smoker	856 (10.9%)	108 (12.4%)	152 (12.2%)	596 (10.4%)

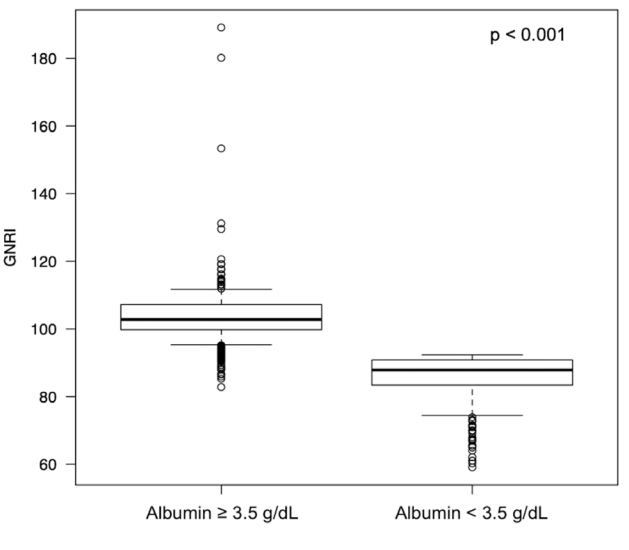
Albumin (g/dL)	4.10 [3.70 - 4.30]	3.10 [2.75 - 3.20]	3.60 [3.50 - 3.70]	4.20 [4.00 - 4.40]
Creatinine (mg/dL)	1.01 [0.84 - 1.30]	1.10 [0.85 - 1.41]	1.04 [0.87 - 1.33]	1.00 [0.83 - 1.25]
Hematocrit (%)	40.00 [36.20 - 43.10]	33.40 [29.60 - 37.50]	38.00 [34.20 - 41.90]	41.00 [37.90 - 43.70]
Platelets (mm^3)	230.00 [189.00 - 282.00]	271.50 [210.75 - 368.25]	234.00 [189.00 - 293.00]	225.00 [187.00 - 272.00]
White blood cells (mm^3)	7.10 [5.90 - 8.60]	7.90 [6.33 - 9.80]	7.30 [6.00 - 8.70]	7.00 [5.80 - 8.40]
Diabetes mellitus	2129 (27.1%)	243 (27.9%)	366 (29.5%)	1520 (26.4%)
Steroid use	290 (3.7%)	34 (3.9%)	49 (3.9%)	207 (3.6%)
Congestive heart failure	79 (1.0%)	29 (3.3%)	14 (1.1%)	36 (0.6%)
Hypertension	6073 (77.2%)	654 (75.0%)	947 (76.3%)	4472 (77.8%)
COPD	481 (6.1%)	70 (8.0%)	95 (7.7%)	316 (5.5%)
Dyspnea at rest/exertion	717 (9.1%)	126 (14.4%)	151 (12.2%)	440 (7.7%)
Preoperative blood transfusion	79 (1.0%)	48 (5.5%)	12 (1.0%)	19 (0.3%)
Bleeding disorder	261 (3.3%)	57 (6.5%)	57 (4.6%)	147 (2.6%)
Disseminated cancer	513 (6.5%)	143 (16.4%)	109 (8.8%)	261 (4.5%)
Preoperative AKI	33 (0.4%)	9 (1.0%)	6 (0.5%)	18 (0.3%)
Dialysis	210 (2.7%)	67 (7.7%)	50 (4.0%)	93 (1.6%)
Nephrectomy type				
Partial	4661 (59.3%)	3076 (53.5%)	859 (69.2%)	726 (83.3%)
Radical	3202 (40.7%)	2674 (46.5%)	382 (30.8%)	146 (16.7%)
Surgical approach				
Robotic/Laparoscopic	2540 (32.3%)	414 (47.5%)	446 (35.9%)	1680 (29.2%)
Open	5323 (67.7%)	458 (52.5%)	795 (64.1%)	4070 (70.8%)
Wound classification				
I - Clean	1653 (21.0%)	199 (22.8%)	256 (20.6%)	1198 (20.8%)
II - Clean/Contaminated	6126 (77.9%)	655 (75.1%)	957 (77.1%)	4514 (78.5%)
III - Contaminated	69 (0.9%)	11 (1.3%)	24 (1.9%)	34 (0.6%)
IV - Dirty/Infected	15 (0.2%)	7 (0.8%)	4 (0.3%)	4 (0.1%)
Operative time (min)	166.00 [122.00 - 219.00]	169.50 [120.75 - 224.25]	169.00 [123.00 - 224.00]	165.00 [123.00 - 217.00]

GNRI = geriatric nutritional risk index; BMI = body mass index; ASA = American Society of Anesthesiologists; 5i-mFI = 5-item modified frailty index; COPD = chronic obstructive pulmonary disease; AKI = acute kidney injury

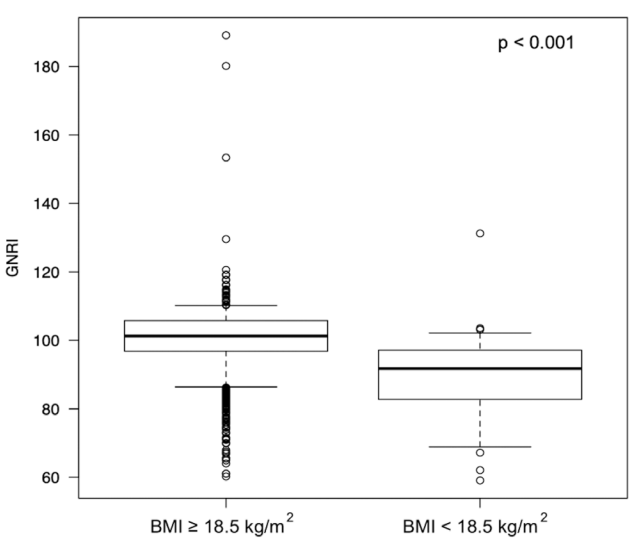
Figure 2 - Boxplots for GNRI score compared to low albumin (< 3.5 g/dL), low BMI (< 18.5 kg/m²), and > 10% body weight loss in the last 6 months prior to nephrectomy.



	Weight loss	
	No	Yes
GNRI (median [IQR])	102.75 [96.79 - 105.73]	91.91 [84.42 - 98.48]



	Serum albumin	
	≥ 3.5 g/dL	< 3.5 g/dL
GNRI (median [IQR])	102.75 [99.77 - 107.22]	87.86 [83.39 - 90.84]



	BMI	
	≥ 18.5 kg/m²	< 18.5 kg/m²
GNRI (median [IQR])	101.26 [96.79 - 105.73]	91.76 [82.93 - 97.04]

jor complications (CD III/IV) were significantly higher in malnourished patients compared to those with a normal nutritional status.

A MLRA for GNRI defined as a categorical variable was performed (Table-3). After controlling for the confounding variables previously mentioned, malnutrition was found to be independently associated with any readmission (moderate malnutrition: OR 1.30, 95% CI 1.03 – 1.64, p = 0.029; severe malnutrition: OR 1.50, 95% CI 1.14

Table 2 - Patient postoperative 30-day outcomes.

Variables	All patients (n=7863)	GNRI <92 (n=872)	GNRI 92-98 (n=1241)	GNRI >98 (n=5750)	p value
Acute Renal Failure	80 (1.0%)	9 (1.0%)	15 (1.2%)	56 (1.0%)	0.8
Any NSQIP Complication	1556 (19.8%)	367 (42.1%)	312 (25.1%)	877 (15.3%)	<0.001
Any Readmission	565 (7.2%)	104 (11.9%)	111 (8.9%)	350 (6.1%)	<0.001
Any Reoperation	196 (2.5%)	27 (3.1%)	34 (2.7%)	135 (2.3%)	0.3
Cardiac Arrest Requiring CPR	43 (0.5%)	7 (0.8%)	12 (1.0%)	24 (0.4%)	0.033
Death (CD V)	61 (0.8%)	18 (2.1%)	15 (1.2%)	28 (0.5%)	<0.001
Deep Incisional SSI	13 (0.2%)	2 (0.2%)	3 (0.2%)	8 (0.1%)	0.6
DVT Requiring Therapy	71 (0.9%)	19 (2.2%)	13 (1.0%)	39 (0.7%)	<0.001
Extended Length of Stay	1529 (19.4%)	322 (36.9%)	304 (24.5%)	903 (15.7%)	<0.001
Major Complications (CD III/IV)	406 (5.2%)	78 (8.9%)	85 (6.8%)	243 (4.2%)	<0.001
Myocardial Infarction	74 (0.9%)	10 (1.1%)	15 (1.2%)	49 (0.9%)	0.4
Non-Home Discharge	581 (7.4%)	165 (18.9%)	131 (10.6%)	285 (5.0%)	<0.001
Organ/Space SSI	54 (0.7%)	10 (1.1%)	8 (0.6%)	36 (0.6%)	0.2
Pneumonia	155 (2.0%)	28 (3.2%)	29 (2.3%)	98 (1.7%)	0.007
Progressive Renal Insufficiency	94 (1.2%)	18 (2.1%)	25 (2.0%)	51 (0.9%)	<0.001
Pulmonary Embolism	53 (0.7%)	15 (1.7%)	11 (0.9%)	27 (0.5%)	<0.001
Sepsis	72 (0.9%)	11 (1.3%)	15 (1.2%)	46 (0.8%)	0.2
Septic Shock	40 (0.5%)	12 (1.4%)	10 (0.8%)	18 (0.3%)	<0.001
Stroke/CVA	26 (0.3%)	4 (0.5%)	3 (0.2%)	19 (0.3%)	0.7
Superficial Incisional SSI	83 (1.1%)	17 (1.9%)	20 (1.6%)	46 (0.8%)	0.001
Transfusions	1039 (13.2%)	290 (33.3%)	207 (16.7%)	542 (9.4%)	<0.001
Unplanned Intubation	104 (1.3%)	25 (2.9%)	25 (2.0%)	54 (0.9%)	<0.001
Urinary Tract Infection	159 (2.0%)	34 (3.9%)	26 (2.1%)	99 (1.7%)	<0.001
Ventilator greater than 48 Hours	84 (1.1%)	24 (2.8%)	15 (1.2%)	45 (0.8%)	<0.001
Wound Disruption	23 (0.3%)	6 (0.7%)	3 (0.2%)	14 (0.2%)	0.072

GNRI = geriatric nutritional risk index; **CPR** = cardiopulmonary resuscitation; **CD** = Clavien-Dindo; **SSI** = surgical site infection; **CVA** = cerebrovascular accident

Table 3 - Multivariable analysis of complications with GNRI as a categorical variable.

Complication	GNRI 92-98		GNRI <92	
	OR [95% CI]	p value	OR [95% CI]	p value
Acute Renal Failure	1.05 [0.56-1.97]	0.9	1.70 [0.75-3.88]	0.20
Any NSQIP Complication	1.10 [0.93-1.31]	0.3	1.35 [1.10-1.65]	**0.004**
Any Readmission	1.30 [1.03-1.64]	**0.029**	1.50 [1.14-1.98]	**0.004**
Any Reoperation	1.06 [0.71-1.58]	0.8	1.09 [0.67-1.77]	0.7
Cardiac Arrest Requiring CPR	0.59 [0.28-1.23]	0.16	1.07 [0.40-2.81]	0.9
Death (CD V)	1.46 [0.75-2.85]	0.3	1.27 [0.61-2.65]	0.5
Deep Incisional SSI	0.65 [0.16-2.61]	0.5	0.86 [0.12-6.08]	0.9
DVT Requiring Therapy	0.97 [0.49-1.90]	0.9	0.60 [0.30-1.20]	0.15
Extended Length of Stay	1.50 [1.27-1.78]	**<0.001**	2.33 [1.91-2.85]	**<0.001**
Major Complication (CD III/IV)	1.17 [0.89-1.54]	0.3	1.09 [0.79-1.52]	0.6
Myocardial Infarction	0.96 [0.52-1.77]	0.9	1.31 [0.60-2.86]	0.5
Non-Home Discharge	1.54 [1.22-1.95]	**<0.001**	2.34 [1.81-3.03]	**<0.001**
Organ/Space SSI	0.89 [0.40-1.99]	0.8	1.29 [0.55-3.03]	0.6
Pneumonia	0.91 [0.58-1.42]	0.7	0.89 [0.53-1.48]	0.6
Progressive Renal Insufficiency	2.08 [1.24-3.49]	**0.006**	2.03 [1.07-3.84]	**0.030**
Pulmonary Embolism	1.37 [0.65-2.91]	0.4	1.89 [0.85-4.23]	0.12
Reintubation	1.42 [0.85-2.37]	0.18	1.30 [0.72-2.35]	0.4
Sepsis	1.12 [0.61-2.08]	0.7	0.84 [0.39-1.82]	0.7
Septic Shock	1.84 [0.80-4.25]	0.15	2.93 [1.21-7.07]	**0.017**
Stroke/CVA	0.55 [0.15-1.93]	0.3	0.75 [0.21-2.66]	0.7
Superficial Incisional SSI	1.77 [1.02-3.08]	**0.044**	2.04 [1.04-3.99]	**0.037**
Transfusions/Intraop/Postop	0.94 [0.75-1.16]	0.5	1.17 [0.93-1.48]	0.18
Urinary Tract Infection	1.10 [0.70-1.73]	0.7	2.10 [1.31-3.35]	**0.002**
Ventilator greater than 48 Hours	0.78 [0.40-1.52]	0.5	1.23 [0.65-2.34]	0.5
Wound Disruption	0.77 [0.21-2.87]	0.7	2.13 [0.70-6.52]	0.19

GNRI as a categorical variable with the reference category as "Normal GNRI".
OR = odds ratio; CI = confidence interval; GNRI = geriatric nutritional risk index; NSQIP = National Surgical Quality Improvement Program; CPR = cardiopulmonary resuscitation; CD = Clavien-Dindo; SSI = surgical site infection; CVA - cerebrovascular accident

– 1.98, p = 0.004), progressive renal insufficiency (moderate malnutrition: OR 2.08, 95% CI 1.24 – 3.49, p = 0.006; severe malnutrition: OR 2.03, 95% CI 1.07 – 3.84, p = 0.030), superficial incisional SSI (moderate malnutrition: OR 1.77, 95% CI 1.02 – 3.08, p = 0.044; severe malnutrition: OR 2.04, 95% CI 1.04 – 3.99, p = 0.037), extended LOS (moderate malnutrition: OR 1.50, 95% CI 1.27 – 1.78, p < 0.001; severe malnutrition: OR 2.33, 95% CI 1.91 – 2.85, p < 0.001), and non-home discharge (moderate malnutrition: OR 1.54, 95% CI 1.22 – 1.95, p < 0.001; severe malnutrition: OR 2.34, 95% CI 1.81 – 3.03, p < 0.001). Any NSQIP complication (OR 1.35, 95% CI 1.10 – 1.65, p = 0.004), septic shock (OR 2.93, 95% CI 1.21 – 7.07, p = 0.017), and UTI (OR 2.10, 95% CI 1.31 – 3.35, p = 0.002) were independently associated with severe malnutrition. None of the other postoperative complications were significantly associated with malnutrition. The 30-day outcomes that were independently associated with moderate and severe malnutrition were also statistically significant for the MLRA models using GNRI as a continuous variable (Figure-3). None of the MLRA models had variables with high multicollinearity (VIF ≥ 2.5).

A sensitivity analysis was performed after excluding 513 (6.5%) patients who had disseminated cancer at the time of nephrectomy (Supplementary Table-1). Progressive renal insufficiency, extended LOS, and non-home discharge remained independently associated with moderate and severe malnutrition. Likewise, septic shock and UTI continued to be independently associated with severe malnutrition. Readmission was independently associated with severe malnutrition only. Superficial incisional SSI was not independently associated with either moderate or severe malnutrition.

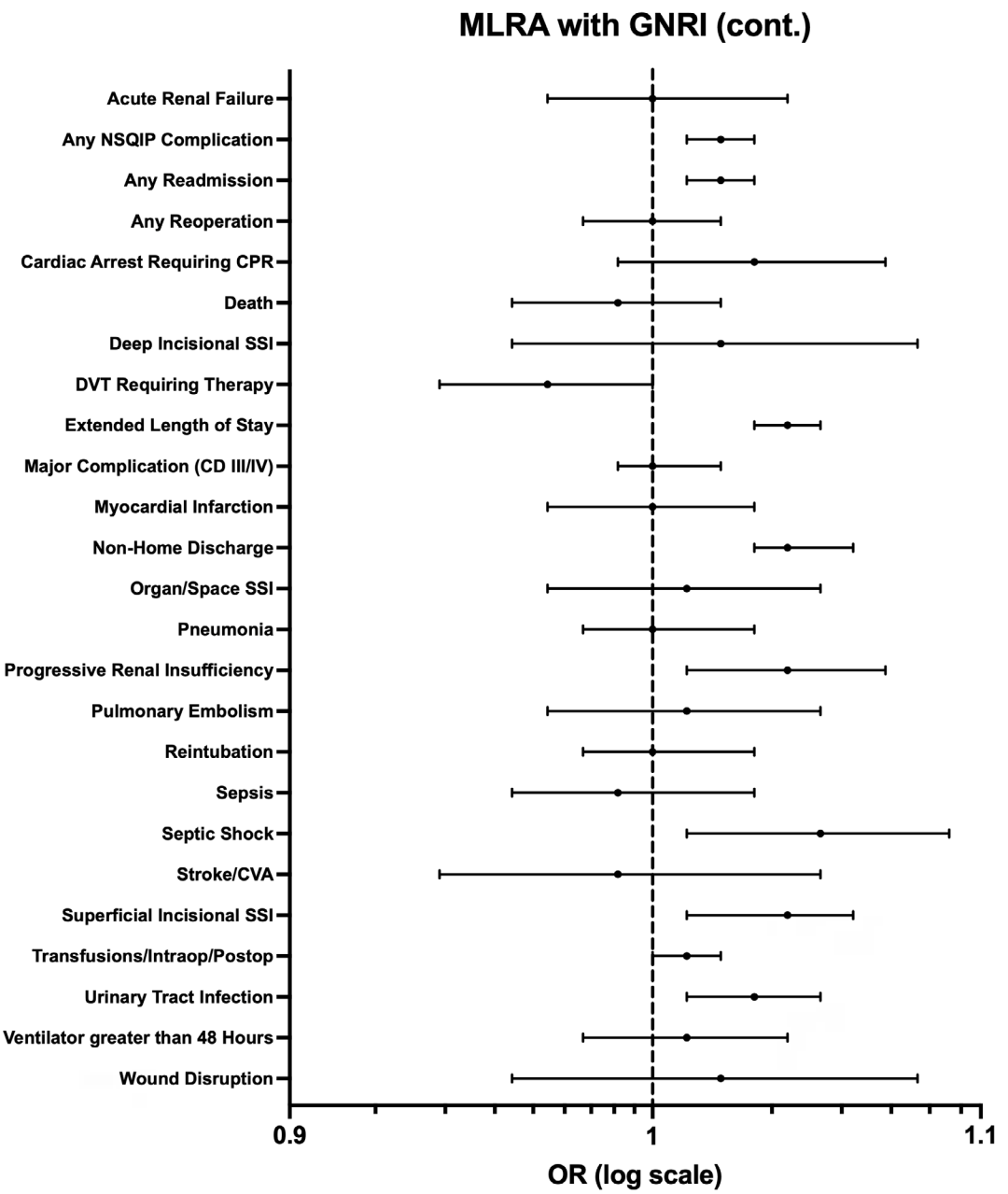
DISCUSSION

Complications after nephrectomy place a significant burden on both the oncological patient and the health care system. The use of predictors for adverse postoperative outcomes is crucial in value-based healthcare as it can aid in better resource management. Although preoperative malnutrition is a well-recognized predictor of poor outcomes following major oncologic surgery, the role of GNRI in evaluating malnutrition and its association with 30-day outcomes following nephrectomy for renal cancer has not been thoroughly studied before (5, 16). As defined by a GNRI ≤ 98, the prevalence of malnutrition in our cohort was 27.3%, which falls within the range of previously reported data (6).

Using MLRA, we found that GNRI was independently associated with readmission, progressive renal insufficiency, superficial incisional SSI, septic shock, UTI, extended LOS, and non-home discharge. After excluding patients with disseminated cancer, the sensitivity analysis yielded similar results with the exceptions of readmission and superficial incisional SSI no longer being independently associated with either moderate or severe malnutrition. This data suggests that malnutrition impacts on 30-day outcomes after nephrectomy, regardless of metastatic disease. The study by May et al. using NSQIP to describe rates of 30-day complications after cytoreductive nephrectomy found malnutrition is not an independent predictor of severe or overall postoperative morbidity; however, their definition was based on a BMI < 18.5 kg/m^2 (24).

Malnutrition is not only associated with poor postoperative outcomes, but also worse long--term survival, quality of life, and chemotherapy toxicity among oncology patients (25, 26). Expert consensus recommends perioperative nutrition screening in elderly patients with the Mini Nutritional Assessment Short Form (MNA-SF) (27). However, this assessment utilizes questions that rely on patient-reported data which translates to poor interobserver reliability. The MNA-SF also requires training to administer, and is not readily available once the patient arrives to the hospital (28). In contrast, the GNRI relies on objective data that could be easily accessible for most patients perioperatively (11). The GNRI also employs a standardized formula that does not require training and could potentially be administered by any health care team member. Gu et al. found that the GNRI was superior to the MNA-SF for risk discrimination regarding overall mortality in patients with renal cancer (14). Other studies have found the GNRI to be an independent predictor of both short

Figure 3 - Multivariable logistic regression analysis for complications after adjusting for covariates. GNRI was classified as a continuous variable (per 1 unit decrease).



OR = odds ratio; GNRI = geriatric nutritional risk index; CPR = cardiopulmonary resuscitation; CD = Clavien-Dindo; SSI = surgical site infection; CVA = cerebrovascular accident

and long-term outcomes following nephrectomy for renal cancer (15, 16).

Although the present study uses a large population to evaluate GNRI as a predictor of complications following nephrectomy, it has inherent limitations that apply to the usage of large clinical databases. First, the NSQIP database limits follow-up to 30 days after the procedure of interest; thus, complications that occur either past 30 days or long-term cannot be analyzed. Second, the cohort is limited to patients with complete anthropometric data and serum albumin measured

within 30 days prior to nephrectomy; this excludes more than 10,000 patients from being potentially included in our study. Third, the general NSQIP file does not collect data on TNM staging, histologic features, or adjuvant therapy, which are prognostic factors that influence outcomes in patients with renal cancer (3, 29, 30). Fourth, NSQIP does not have data on nephrectomy-specific complications which hinders a more granular analysis of postoperative complications. Our findings could be more accurately evaluated in prospective studies, which should systematically include the assessment of the missing variables in question.

CONCLUSIONS

In the setting of nephrectomy for renal cancer, a GNRI ≤ 98 is an independent predictor of 30-day readmission, progressive renal insufficiency, superficial incisional SSI, septic shock, UTI, extended LOS, and non-home discharge. GNRI could be used to assess nutritional status in elderly patients with renal cancer and counsel them prior to nephrectomy.

ABBREVIATIONS

MI = minimally invasive
GNRI = Geriatric Nutritional Risk Index
ACS-NSQIP = American College of Surgeons National Surgical Quality Improvement Program
ICD = International Coding of Diseases
CPT = Current Procedural Terminology
ASA = American Society of Anesthesiology
BMI = body mass index
5i-Mfi = 5-item modified frailty index
DM = diabetes mellitus
HT = hypertension
CHF = congestive heart failure
COPD = chronic obstructive pulmonary disease
CBW = current body weight
IBW = ideal body weight
PE = pulmonary embolism
DVT = deep venous thrombosis
UTI = urinary tract infection
SSI = surgical site infection
CD = Clavien-Dindo
LOS = length of stay
IQR = interquartile range
MLRA = Multivariable logistic regression analysis

DISCLOSURE

The American College of Surgeons National Surgical Quality Improvement Program and the hospitals participating in the ACS NSQIP are the source of the data used herein; they have not verified and are not responsible for the statistical validity of the data analysis or the conclusions derived by the authors.

ETHICS APPROVAL

This study was deemed exempt from ethics approval as the database used contains deidentified data.

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

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Validation of the Vancouver Symptom Score Questionnaire for bladder and bowel dysfunction for Brazilian children and adolescents

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ABSTRACT

Objective: This study aimed to translate, and perform a cross-cultural adaptation, and validation of the Vancouver Symptom Score (VSS) for bladder and bowel dysfunction (BBD) for Brazilian children and adolescents

Materials and Methods: Six steps were performed for the translation and cross-cultural adaptation: (1) translation, (2) synthesis of translations, (3) back-translation, (4) pre-final version of the translated instrument, (5) pilot test and degree of comprehensibility and (6) elaboration of the Brazilian version of the VSS. For validation, the Brazilian Dysfunctional Voiding Score (DVSS) questionnaire was used.

Results: Validation was performed on a sample of 107 children and adolescents with a mean age of 9.2 ± 2.84 years, presenting BBD and 107 without BBD (control group-CG). There was a positive correlation ($r = 0.91$, 95% CI 0.88 to 0.93, $p < 0.0001$) between total VSS score and total DVSS score. VSS was higher in patients with BBD ($p < 0.0001$). The internal consistency estimated by Cronbach's alpha was 0.87 for patients with BBD. The VSS showed excellent diagnostic accuracy in detecting cases, with an area under the ROC curve of 98% (95% CI 0.96 to 0.99, $p < 0.001$). A cut-off value of >11 points produced a sensitivity of 100% (95% CI 96.4% to 100%) and a specificity of 91.8% (95% CI 85.1% to 95.6%).

Conclusion: The translated, cross-culturally adapted, and validated VSS for the Brazilian population is a reliable and valid tool to identify symptoms of BBD in children and adolescents aged five to 16 years, whose first language is Brazilian Portuguese.

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INTRODUCTION

Bladder bowel dysfunction (BBD) comprises lower urinary tract dysfunction (LUTD) and bowel dysfunction (1-3). It represents approximately 40% of patients seen in pediatric urology clinics (3, 4). BBD can be associated with vesicoureteral reflux and recurrent urinary tract infections sometimes leading to renal scarring (5). Symptoms affect the quality of life of children and adolescents, resulting in low self-esteem, social isolation and can lead to impaired learning (6).

Early recognition and non-invasive management of BBD in children and adolescents in a general outpatient setting plays an important role in reducing morbidity (5, 7). Several validated voiding scales are useful for this purpose (3, 5), including the Dysfunctional Voiding Symptom Score (DVSS) (8) and the Vancouver Symptom Score (VSS) (9). Scored questionnaires help diagnosis, allow measurement of severity, and monitor the effectiveness of treatment (3, 5, 10).

The VSS is an instrument that has undergone a careful validation process in the original development phase and uses appropriate measurement properties. It is a short questionnaire that addresses BBD in children and adolescents aged four to 16 years old, with a well-established cut-off value indicating its diagnostic accuracy. The VSS proved to be a valid and reliable tool for identifying BBD in children and adolescents and can be used both in clinical practice and research (9, 11). Drzewiecki et al. showed that VSS could be a diagnostic support tool for BBD and a way to assess treatment effectiveness (12).

Although the translated and cross-culturally adapted version of the DVSS questionnaire for the Brazilian population (13) has proved to be a valuable tool for screening and diagnosing BBD, it does not contain questions about enuresis if compared to VSS. In addition, the way in which the intensity of the investigated symptoms is graded presents great difficulty in application and interpretation. Besides, recently, the translation and cross-cultural adaptation of the Childhood Bladder and Bowel Dysfunction Questionnaire (CBBDQ) was carried out, which will allow the quantitative assessment of BBD in Brazilian children, but it can only be applied up to 12 years of age and a cutoff point was not yet defined for diagnostic purposes (14).

Using the DVSS and VSS instruments, we hypothesized that patients with BBD would have higher VSS scores than children and adolescents without BBD. In addition, patients with higher VSS scores would also have increased DVSS scores. Therefore, in this context, the objective of the present study was to carry out the process of translation, cross-cultural adaptation, and validation of the English version of the VSS for safe use in clinical practice and scientific research in the Brazilian population.

MATERIALS AND METHODS

Ethical approval

The institution's Ethics Committee approved the study under protocol CAAE 39015220.0.0000.5149, position statement 4.487.157. Legal guardians and participants aged 10 and 16 years signed the Informed Consent Term and the Assent Term, respectively. The corresponding author of the original study authorized the translation, cross-cultural adaptation, and validation of the VSS for the Brazilian population.

Instrument

Vancouver Symptom Score (VSS)

The VSS instrument was built as a self-administered questionnaire. All items were weighted equally. The questionnaire has 13-item condition-specific measures to assess symptoms of BBD (ten of bladder symptoms and three of bowel symptoms). A five-point Likert scale is used for all questions. Each question refers to a single symptom. A score of zero represents no complaints, while a score of four indicates severe symptoms. Only the question three about voiding frequency is scored different from other questions to establish voiding frequency abnormalities. The neutral choice (five to six urination per day) scored zero. Urinary frequency of one to two times or more than eight times a day has a score of four. Urinary frequency of three or four and seven or eight times a day corresponds to a score of two. The instrument total score ranges from zero to 52, being higher sco-

res indicative of more severe symptoms. A total score of 11 was associated with 80% sensitivity and 91% specificity for symptoms of BBD. There is still one more question (item 14) that addresses feedback regarding the facility or not in completing the questionnaire and is not included in the total score (9) (Figure-1).

Study design

The study was conducted following a biphasic validation methodology.

Stage 1: The translation into Brazilian Portuguese and the cross-cultural adaptation for the Brazilian population (15-18).

Stage 2: Validation of the translated and cross-culturally adapted instrument in a sample of Brazilian children and adolescents (15, 18-21).

Flowchart with the steps involved in the translation, cross-cultural adaptation, and validation of the VSS questionnaire is shown in Figure-2.

Stage 1: The translation and the cross-cultural adaptation (15-18)

A group of eight health professionals, composed of physicians and a physical therapist with extensive experience in pediatric urology participated in this six-phase stage.

Phase 1: The translation for Brazilian Portuguese

Two physicians, whose native language is Brazilian Portuguese and who were fluent in English, independently translated the original VSS questionnaire into Brazilian Portuguese. Two translated versions (T) of the questionnaire were generated: T1 and T2.

Phase 2: Synthesis of translations

A meeting was held between the two translators who participated in Phase 1 and the team of experts. This group of professionals produced the synthesized direct translation nominated T3 based on the evaluation, reflection, and discussion.

Phase 3: Back-translation

The T3 was then independently back--translated (R1) into English by a bilingual translator. This translator did not participate in the first phase, was not a health professional, and was not informed about the concepts explored by the instrument. The translation was performed without prior knowledge of the original version of the questionnaire.

Phase 4: Pre-final version of the translated questionnaire

The committee of experts analyzed the versions generated in the previous stages (T1, T2, T3 and R1) and compared them with the original questionnaire. After consensus, the translated versions were edited and consolidated in the joint development of the pre-final version of the VSS questionnaire for Brazilian Portuguese nominated T4.

Phase 5: Pilot testing the pre-final version and evaluation of the degree of understanding

According to the protocol described by Beaton et al. (15), the primary researcher applied the pre-final version (T4) to 35 people randomly selected from different age groups and educational levels. The guiding question for the evaluation of the T4 version was: "Did you understand what was asked?" with the answer being YES or NO. Participants could request the researcher's mediation in case of difficulty.

Phase 6: Final version

A committee of experts analyzed the results of the pilot test. The necessary changes were made according to the difficulties encountered by the participants of the previous phase. After consensus, the final version nominated T5 of the questionnaire was prepared: the Brazilian version of the VSS (Figure-3).

Stage 2: Validation the Brazilian version of the VSS in a sample of Brazilian children and adolescents (15, 18-21)

Study population

Inclusion criteria

The study group consisted of 126 consecutive children and adolescents with 5 to 16 years old, diagnosed with BBD, and who regularly attended a specialized LUTD outpatient clinic from January

Figure 1 – Vancouver Symptom Score (VSS) for Bladder Bowel Dysfunction adapted from Afshar et al. 2009 (9).

1 – I pee in my underwear during the day:

Never | 1 day a week | 2-3 days a week | 4-5 days a week | Everyday

2 – When I pee in my underwear, they are:

In don't pee in | Almost dry | Damp | Wet | Soaked

3 – In a normal day I go to the washroom to pee:

1-2 times | 3-4 times | 5-6 times | 7-8 times | More than 8 times

4 – I feel that I have to rush to the washroom to pee:

Never | Less than half of the time | Half of the time | More than half oh the time | Everyday

5 – I hold my pee by crossing my legs or sitting down

Never | Less than half of the time | Half of the time | More than half oh the time | Everyday

6 – It hurts when I pee:

Never | Less than half of the time | Half of the time | More than half oh the time | Everyday

7 – I wet my bed at night:

Never | 3-4 nights per month | 1-2 nights per week | 4-5 nights per week | Every night

8 – I woke up to pee at night:

Never | 3-4 nights per month | 1-2 nights per week | 4-5 nights per week | Every night

9 – When I pee, it stops and starts:

Never | Less than half of the time | Half of the time | More than half oh the time | Everyday

10 – I have to push or wait for my pee to start:

Never | Less than half of the time | Half of the time | More than half oh the time | Everyday

11 – I have bowel movements (poop):

More than once per day | Every day | Every other day | Every 3 days | More than every 3 days

12 – My stool (poop) is hard:

Never | Less than half of the time | Half of the time | More than half oh the time | Everyday

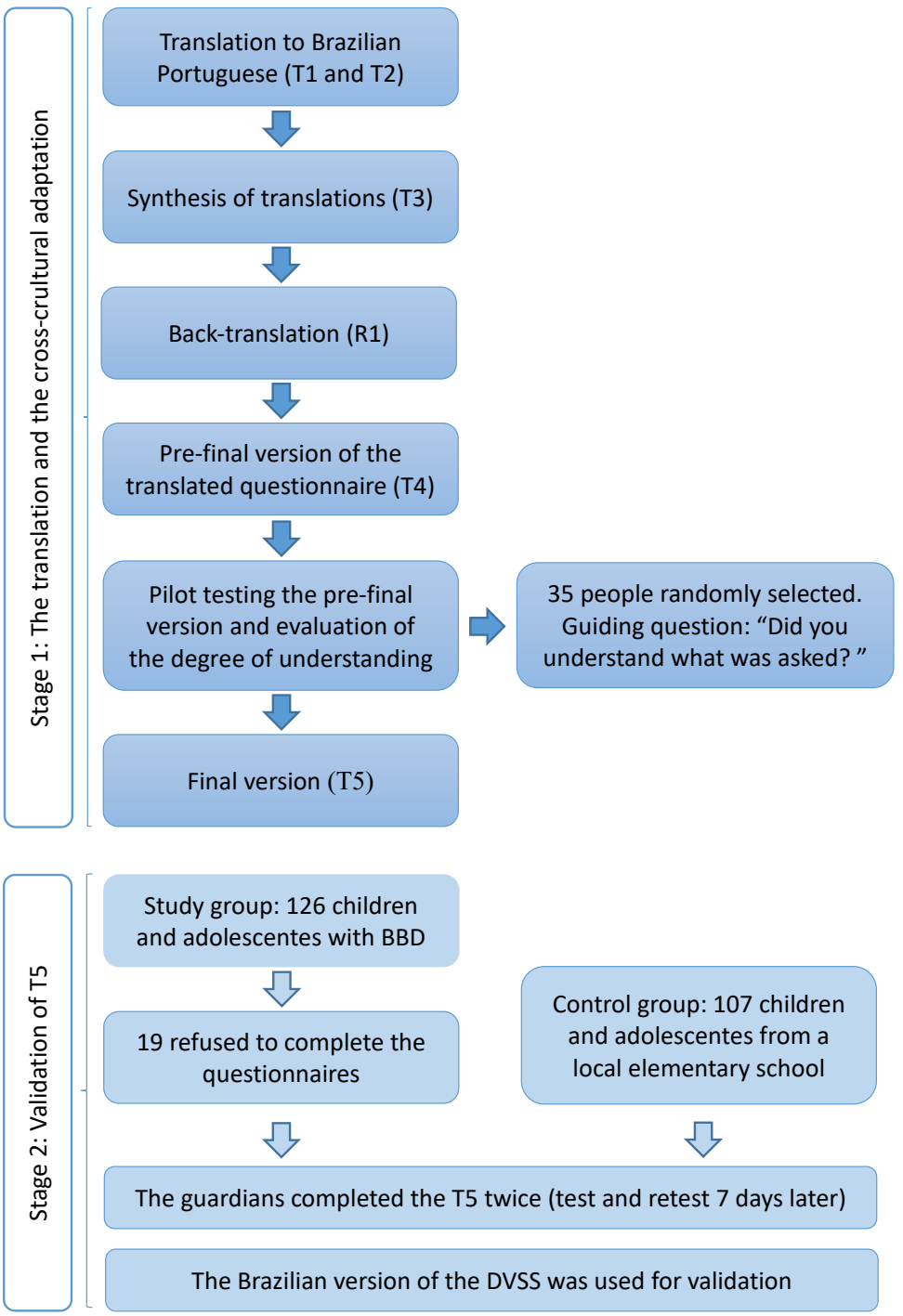
13 – I have bowel (poop) accidents in my underwear:

Never | 1-2 times per week | 3 times per week | 4-5 times per week | Everyday

14 – How easy was to answer these questions?

Very easy | Easy | Neither easy or difficult | Difficult | Very difficult

Figure 2 – Flowchart with the steps involved in the translation, cross-cultural adaptation, and validation of the Vancouver Symptom Score (VSS) (15-21).



VSS = Vancouver Symptom Score; T1 = translated version 1; T2 = translated version 2; T3 = synthesized translated version; R1 = back-translated version; T4 = pre-final version; T5 = final version; BBD = Bladder bowel dysfunction; DVSS = Dysfunctional Voiding Symptom Score

Figure 3 – Brazilian version of the Vancouver Symptom Score (VSS).

1 – Você faz xixi na roupa (cueca/calcinha) durante o dia?

Nunca | 1 vez/semana | 2-3 vezes/semana | 4-5vezes/semana | Todo dia

2 – Quando você molha a roupa (cueca/calcinha) com xixi, você fica?

Não molho | Quase seco | Úmido | Molhado | Encharcado

3 – Num dia normal, quantas vezes você vai ao banheiro para fazer xixi?

1-2 vezes | 3-4 vezes | 5-6 vezes | 7-8 vezes | Mais de 8 vezes

4 – Quando você tem vontade de fazer xixi, você sente necessidade de correr para o banheiro?

Nunca | Raramente | Metade das vezes | Frequentemente | Sempre

5 – Quando você sente vontade de fazer xixi, você cruza as pernas ou agacha para prender o xixi?

Nunca | Raramente | Metade das vezes | Frequentemente | Sempre

6 – Quando você faz xixi, você sente dor?

Nunca | Raramente | Metade das vezes | Frequentemente | Sempre

7 – Você faz xixi na cama enquanto dorme?

Nunca | Menos de 1 noite/semana | 1-2 noites/semana | 4-5 noites/semana | Sempre que dorme

8 – Você acorda e vai ao banheiro fazer xixi no meio da noite?

Nunca | Menos de 1 noite/semana | 1-2 noites/semana | 4-5 noites/semana | Toda noite

9 – Quando você está fazendo xixi, seu jato é interrompido (para e começa de novo)?

Nunca | Raramente | Metade das vezes | Frequentemente | Sempre

10 – Quando você vai começar a fazer xixi, você precisa fazer força ou ficar esperando para o xixi sair?

Nunca | Raramente | Metade das vezes | Frequentemente | Sempre

11 – Você faz cocô:

Mais de uma vez ao dia | Todo dia | Dia sim / Dia não (De 2 em 2 dias) | A cada 3 dias | Com intervalos maiores que 3 dias

12 – Quando você faz cocô, suas fezes são duras?

Nunca | Raramente | Metade das vezes | Frequentemente | Sempre

13 – Você faz cocô na roupa (cueca/calcinha)?

Nunca | 1 a 2 vezes por semana | 3 vezes por semana | 4 a 5 vezes por semana | Todo dia

14 – Este questionário foi fácil de responder?

Muito fácil | Fácil | Nem fácil, nem difícil | Difícil | Muito difícil

2021 to July 2022. The control group (CG) was composed of children and adolescents without a diagnosis or symptoms of BBD from a local school randomly approached to participate in the study, matched by gender, age, and socioeconomic status with the cases.

Exclusion criteria

Children and adolescents with intellectual development disorders, congenital anomalies of the nervous system, urogenital malformations, presence of diseases and/or use of medications that interfere with the functioning of the bladder or urethral sphincter or that refused to participate in the study.

Sample Calculation

There is no consensus on the ideal sample size for validation studies. Terwee et al. (19) stated that criteria for the sample size needed for studies that assess measures were not defined. Rules-of-thumb vary from four to 10 subjects per variable, with a minimum number of 100 subjects (22).

Validation

Of the 126 study group participants, 19 refused to complete the questionnaires. The final sample was 107 patients with BBD. Similarly, 107 controls were invited to complete the questionnaire.

The parents (or caregivers) completed the questionnaire of children aged five to nine years old and adolescents aged 10 to 16 years old completed the questionnaire to measure completion times. A researcher used a stopwatch and recorded the time in minutes spent individually on the task. The completion of the questionnaire seven days after the first application assessed test-retest reliability.

For validation, the Brazilian version of the DVSS (13) was used (Supplementary Table-1). The cut-off values to indicate the presence of BBD were > six for females and > nine for males

Statistical analysis

Psychometric properties

In accordance with the recommendations for the cross-cultural adaptation process, the following psychometric properties of the VSS questionnaire were evaluated in our study (15-19):

1. Reliability: In this study, measurement properties, internal consistency and test-retest reliability were evaluated. Internal consistency was evaluated by the Cronbach coefficient, when be greater than 0.7 indicates good internal consistency. A correlation above 0.7 in test-retest reliability indicates good internal consistency. Test-retest reliability was estimated by Pearson's correlation coefficient (19).

2. Validity: In this study, we evaluated the construct validity of measure and content properties. Pearson's correlation test compared the questionnaires VSS and DVSS.

Quantitative variables were expressed as medians and interquartile ranges, while qualitative variables were expressed as absolute values, percentages, or proportions. P values < 0.05 were considered statistically significant.

The software GraphPad Prism, version 9.0.3 (GraphPad Prism®, San Diego-CA, USA) was used for statistical analysis.

RESULTS

The study group comprised 107 children and adolescents with the same number in control group. In both groups, parents or caregivers completely answered the VSS and DVSS questionnaires (Table-1).

There was a positive correlation ($r = 0.91$, 95% CI 0.88 to 0.93, $p < 0.0001$) between total VSS score and total DVSS score (Figure-4).

The mean score for VSS in patients with BBD was 22, while in controls the same parameter was 2 ($p < 0.0001$) (Figure-5).

All participants (study and control group) rated the questionnaire as easy or very easy to answer. The mean time to complete the questionnaire was 3 minutes (ranging from two to six minutes).

The internal consistency estimated by Cronbach's alpha was 0.87 for BBD (95% lower confidence limit 0.85 to 0.82). We evaluated test--retest reliability in 97 cases and controls. The response rate was 93%, and the Pearson correlation

Table 1 - Sociodemographic characteristics of the children and adolescents with Bladder Bowel Dysfunction (BBD) and Control Group

Characteristics	Children and adolescentes with BBD (n=107)	Control group (n=107)	p-value
Gender			**0.12**
Male	52.3 (56/107)	52.3 (56/107)	
Female	47.7 (51/107)	47.7 (51/107)	
Mean Age years (SD)	9.2±2.84	9.6±2.98	0.09
Age Range years	(5.1-16)	(5.7-16)	
Socioeconomic status			**0.1**
Categories A and B	36.4% (39/107)	43.9% (47/107)	
Categories C, D and E	63.3% (68/107)	56.1% (60/107)	

BBD = Bladder bowel dysfunction; p value = Unpaired t test; SD = Standard deviation

coefficient was 0.94 (p<0.001), showing excellent reliability when the two questionnaires were answered one week apart.

VSS had excellent diagnostic accuracy in detecting BBD, with an area under the Receiver Operating Characteristic (ROC) curve (AUC) of 98% (95% CI: 0.96 to 0.99, p < 0.001) (Figure-6).

The cut-off value above 11 points yielded a sensitivity of 100% (95% CI 96.4% to

Figure 4 - Correlation between total Vancouver Symptom Score (VSS) score and total Disfunction Voiding Symptom Score (DVSS) score.

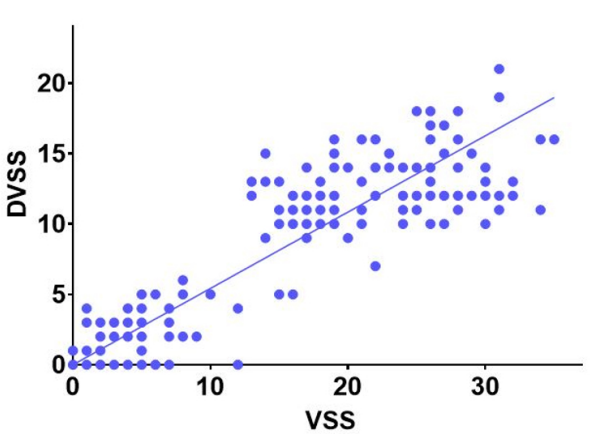


Figure 5 - Median Vancouver Symptom Score (VSS) score in cases and controls.

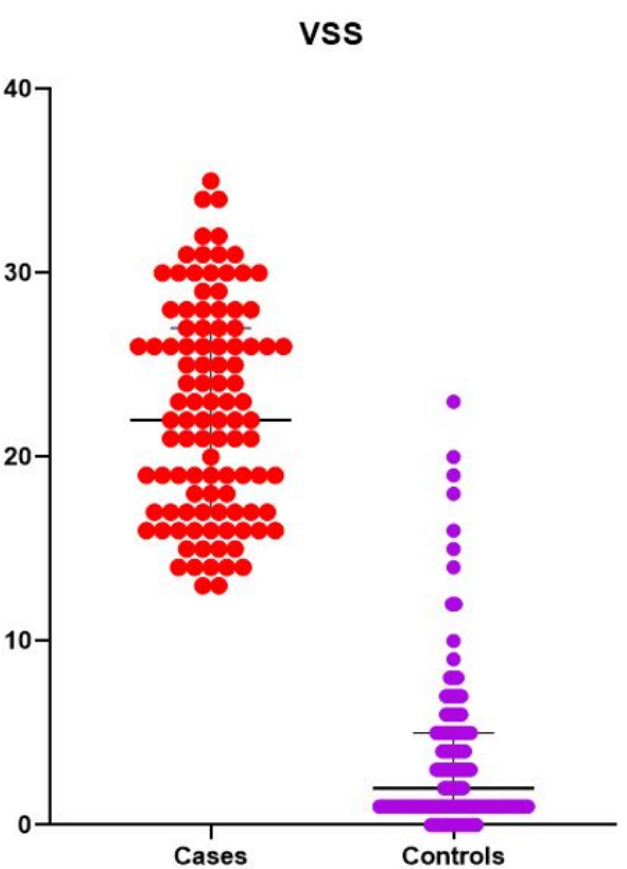
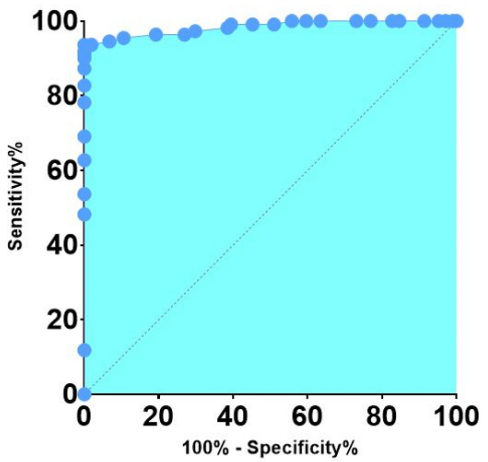


Figure 6 – ROC curve for Vancouver Symptom Score (VSS).



ROC Receiver Operating Characteristic

100%) and a specificity of 91.8% (95% CI 85.1% to 95.6%) with Likelihood ratio of 12.2. (Supplementary Table-2).

DISCUSSION

This study reported the authorized translation, cross-cultural adaptation, and validation of the VSS to be used in Brazilian children and adolescents with BBD. The excellent comprehension values achieved during pre-test applications of the translated VSS in participants whose first language is Brazilian Portuguese showed that the translated scale was adequately adapted to the Brazilian culture. In addition, there were robust evidence of validity and reliability in this sample.

Translation and cultural adaptation are vital steps. In addition to language, cultural aspects considerably influence the understanding of an instrument. Therefore, the cross-cultural adaptation of the original components is necessary (15-18). The sequential phases of translation, back-translation and meetings between the translators and the team of specialists led to the development of descriptions adapted to a better understanding by the parents and Brazilian children and adolescents (15, 23, 24).

In the present study, a high correlation between VSS and DVSS was found. DVSS was chosen since it is one of the most used instruments for the evaluation of BBD symptoms and has already been validated in Brazilian population (13). We hypothesized that a significant correlation between VSS and DVSS would be found. Indeed, we detected a high positive correlation between the two questionnaires. Thus, data from the control group confirmed the potential of the VSS to differentiate between participants with and without symptoms of BBD. The BBD group had significantly higher scores than the control group, indicating a discriminative ability and possible diagnostic value of VSS for children and adolescents with BBD. In the analysis of internal consistency, a Cronbach's alpha of 0.87 in the patients' group indicated good level of internal consistency. The value obtained was superior to the Cronbach's alpha (0.45) (9) described in the original validation study and the Dutch validation of the VSS (0.55) (11).

Excellent test-retest reliability was also found (Pearson coefficient 0.94), similar to the original study (0.89) (9) and better than the Dutch VSS validation study (0.41) (11). We chose a week to repeat the test. In line with the original research, it is unlikely that the symptoms of BBD will change in such a short amount of time, even though we have initiated or prescribed treatment modifications. Furthermore, repeated responses were rarely based solely on recall of the first questionnaire (9). The retest in the Dutch study was carried out within 15 days, and they made general recommendations related to voiding and bowel function at baseline. Thus, the authors found that this determined some improvement in BBD symptoms within 15 days. Therefore, by selecting only patients whose test-retest period was one week, the Dutch version of the VSS showed adequate reliability and test-retest (0.79- 0.94) (11).

In our study, the VSS had excellent diagnostic accuracy in detecting patients with BBD, with an AUC of 98%. A cut-off scores above 11 points had a diagnostic sensitivity of 100% and a specificity of 91.61%. This finding is supported by the study of Asfhar et al., (9) in which the AUC was of 98%. The authors also showed that a score of 11 had diagnostic sensitivity and specificity of 80% and 91%, respectively. The high sensitivity and specificity of the VSS questionnaire indicate that this instrument is a valuable screening tool, since it allows the early identification and referral of children and adolescents with symptoms of BBD

to specialized centers (3, 5, 7, 9-11). The early diagnosis and adequate multidisciplinary treatment can avoid the repercussions for the upper urinary tract mainly represented by renal scars (5). Additionally, the treatment can improve self-esteem and the quality of family, school, and social life (6).

All participants with BBD and controls rated the questionnaire as easy or very easy to answer and took a few minutes to complete the questionnaire. These data are similar to those obtained in the study of Asfhar et al. (9) in which 85% of the participants classified the questionnaire as easy or very easy to answer.

The major limitation of the present study is that the VSS was not tested to detect changes after different treatments, that is, an analysis of responsiveness. Future research should focus on the responsiveness and clinical applicability of the Brazilian version of the VSS.

BBD is a common condition in the urology practice and often appears subjective to the attending physician's judgment. The lack of a validated instrument to diagnose this condition negatively impacts clinical practice and research, creating a heterogeneous patient population across different studies and, consequently, inconsistent results. We have chosen the VSS because this instrument is short, easy to apply, well established in the literature for the diagnose of BBD, and superior to other scores used in our population. The validation of VSS is an essential issue to use this questionnaire in Brazilian population.

CONCLUSION

The Vancouver Symptom Score translated, cross-culturally adapted, and validated for the Brazilian population seems to be a reliable and valid tool to identify symptoms of bladder bowel dysfunction in children and adolescents aged five to 16 years whose first language is Brazilian Portuguese. The authors believe that this version will be helpful for clinical practice and scientific research in Brazil.

ABBREVIATIONS

AUC = Area under the ROC Curve
BBD = Bladder bowel dysfunction
CBBDQ = Childhood Bladder and Bowel Dysfunction Questionnaire
DVSS = Dysfunctional Voiding Symptom Score
LUTD = Lower urinary tract dysfunction (LUTD)
VSS = Vancouver Symptom Score
ROC = Receiver Operating Characteristic (ROC)

COMPLIANCE WITH ETHICAL STANDARDS

The institution's Ethics Committee approved the study under protocol CAAE 39015220.0.0000.5149, position statement 4.487.157. Legal guardians and participants aged 10 and 16 years signed the Informed Consent Term and the Assent Term, respectively. The corresponding author of the original study authorized the translation, cross-cultural adaptation, and validation of the VSS for the Brazilian population.

The data that support the findings of this study are available from the corresponding author. Data will be made available upon request

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CONFLICT OF INTEREST

None declared.

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APPENDIX

Supplementary table 1 - Brazilian version of the Dysfunctional Voiding Symptom Score (DVSS) adapted from Calado et al. 2010 (13).

Durante os últimos 30 dias	Nunca ou Quase nunca	Menos Que Metade do Tempo	A Metade do tempo	Quase Todo o Tempo
1. Seu(a) filho(a)tem molhado de xixi a roupa durante o dia?	0	1	2	3
2. Quando seu(a) filho(a) se molha de xixi, a cueca ou calcinha fica ensopada?	0	1	2	3
3. Com que frequência seu(a) filho(a) não faz cocô todos os dias?	0	1	2	3
4. Seu(a) filho(a) tem que fazer força para fazer cocô?	0	1	2	3
5. Com que frequência seu(a) filho(a) só vai ao banheiro fazer xixi uma ou duas vezes por dia?	0	1	2	3
6. Seu(a) filho(a) segura o xixi cruzando as pernas, agachando ou dançando?	0	1	2	3
7. Quando seu(a) filho(a) precisa fazer xixi tem que ir rápido ao banheiro? (não consegue esperar)	0	1	2	3
8. Seu(a) filho(a) tem que fazer força para fazer xixi?	0	1	2	3
9. Seu(a) filho(a) disse que sente dor quando faz xixi?	0	1	2	3
10. 10. Seu(a) filho(a) passou por alguma situação estressante como as dos exemplos abaixo nos últimos 30 dias? Marque ao lado sim ou não.				
• Bebê novo em casa				
• Mudança de casa				
• Mudança de escola				
• Problemas escolares				
• Abuso(sexual/físico)		Não (0)		Sim (3)
• Problemas em casa (divórcio/morte)				
• Eventos especiais (aniversário)				
• Acidente/ferimento				
• Outros				

Supplementary Table-2. Details of the specificity and sensitivity of the Vancouver Symptom Score (VSS) scores.

	Sensitivity%	95% CI	Specificity%	95% CI	Likelihood ratio
> 0.5000	100.0	96.44% to 100.0%	11.82	7.038% to 19.18%	1.134
> 1.500	100.0	96.44% to 100.0%	48.18	39.06% to 57.42%	1.930
> 2.500	100.0	96.44% to 100.0%	53.64	44.35% to 62.67%	2.157
> 3.500	100.0	96.44% to 100.0%	62.73	53.41% to 71.19%	2.683
> 4.500	100.0	96.44% to 100.0%	69.09	59.93% to 76.96%	3.235
> 5.500	100.0	96.44% to 100.0%	78.18	69.58% to 84.88%	4.583
> 6.500	100.0	96.44% to 100.0%	82.73	74.59% to 88.65%	5.789
> 7.500	100.0	96.44% to 100.0%	87.27	79.76% to 92.27%	7.857
> 8.500	100.0	96.44% to 100.0%	90.00	82.98% to 94.32%	10.00
> 9.500	100.0	96.44% to 100.0%	90.91	84.07% to 94.99%	11.00
> 11.00	100.0	96.44% to 100.0%	91.82	85.18% to 95.64%	12.22
> 12.50	100.0	96.44% to 100.0%	93.64	87.44% to 96.88%	15.71
> 13.50	98.08	93.26% to 99.66%	93.64	87.44% to 96.88%	15.41
> 14.50	93.27	86.75% to 96.70%	94.55	88.61% to 97.48%	17.10
> 15.50	89.42	82.05% to 93.99%	95.45	89.80% to 98.04%	19.67
> 16.50	80.77	72.15% to 87.19%	96.36	91.02% to 98.58%	22.21
> 17.50	73.08	63.84% to 80.67%	96.36	91.02% to 98.58%	20.10
> 18.50	70.19	60.81% to 78.14%	97.27	92.29% to 99.26%	25.74
> 19.50	61.54	51.94% to 70.32%	98.18	93.61% to 99.68%	33.85
> 20.50	60.58	50.97% to 69.43%	99.09	95.03% to 99.95%	66.63
> 21.50	54.81	45.24% to 64.03%	99.09	95.03% to 99.95%	60.29
> 22.50	49.04	39.64% to 58.51%	99.09	95.03% to 99.95%	53.94

CI = Confidence Interval

ORIGINAL ARTICLE

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Comparing the outcomes of robotic assisted radical prostatectomy in black and white men: Experience of a high-volume center

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ABSTRACT

Background: Global cancer incidence ranks Prostate Cancer (CaP) as the second highest overall, with Africa and the Caribbean having the highest mortality. Previous literature suggests disparities in CaP outcomes according to ethnicity, specifically functional and oncological are suboptimal in black men. However, recent data shows black men achieve post radical prostatectomy (RP) outcomes equivalent to white men in a universally insured system. Our objective is to compare outcomes of patients who self-identified their ethnicity as black or white undergoing RP at our institution.

Materials and methods: From 2008 to 2017, 396 black and 4929 white patients underwent primary robotic-assisted radical prostatectomy (RARP) with a minimum follow-up of 5 years. Exclusion criteria were concomitant surgery and cancer status not available. A propensity score (PS) match was performed with a 1:1, 1:2, and 1:3 ratio without replacement. Primary endpoints were potency, continence recovery, biochemical recurrence (BCR), positive surgical margins (PSM), and post-operative complications.

Results: After PS 1:1 matching, 341 black vs. 341 white men with a median follow-up of approximately 8 years were analyzed. The overall potency and continence recovery at 12 months was 52% vs 58% (p=0.3) and 82% vs 89% (p=0.3), respectively. PSM rates was 13.4 % vs 14.4% (p = 0.75). Biochemical recurrence and persistence PSA was 13.8% vs 14.1% and 4.4% vs 3.2% respectively (p=0.75). Clavien-Dindo complications (p=0.4) and 30-day readmission rates (p=0.5) were similar.

Conclusion: In our study, comparing two ethnic groups with similar preoperative characteristics and full access to screening and treatment showed compatible RARP results. We could not demonstrate outcomes superiority in one group over the other. However, this data adds to the growing body of evidence that the racial disparity gap in prostate cancer outcomes can be narrowed if patients have appropriate access to prostate cancer management. It also could be used in counseling surgeons and patients on the surgical intervention and prognosis of prostate cancer in patients with full access to gold-standard screening and treatment.

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INTRODUCTION

Global cancer statistics (GLOBOCAN 2020) (1) have ranked prostate cancer (CaP) as the third highest organ site for new cases and the third highest cause of death due to cancer among both genders. In men specifically, CaP is second to lung cancer in incidence, with Africa and the Caribbean having the highest mortality due to the former. The literature has suggested that racial disparity in CaP outcomes exists owing to differences in socioeconomics, access to healthcare (2); genetic profiles (3), pathological upstaging after radical prostatectomy (RP) (4), and surgical acumen (5). Previous studies have reported that the functional and oncological outcomes are suboptimal in black men, and as a result, their CaP management requires a refined approach (6).

Parry et al. (7) confirmed in a UK National CaP Audit that the likelihood of receiving radical treatment was higher in more affluent, lower comorbid, and non-black patients. The comparative outcomes per ethnic category are awaited as the evidence of comparable response to standard of care CaP treatment increases. Cole et al. (8) analyzed data from Massachusetts, US, to investigate comparative time to definitive treatment within 90 days of diagnosis (RP or radiation therapy [RT]) and cancer-specific survival. The study found that black men received less definitive treatment and had lower cancer-specific mortality than white men, concluding that both ethnic groups achieved equivalent outcomes in universally insured health locations. This is supported by a meta-analysis of seven randomized clinical trials (9), where the response of black men to radiotherapy (RT) was superior to white men. Considering the above, CaP management should result in equivalent or even superior outcomes in black men compared to matched groups in some circumstances.

The increased use of robotic approaches has favorably impacted the urinary and sexual function profile of patients compared to open and laparoscopic surgery (10). Additionally, the intra and postoperative complication rates are less with RARP than with open RP (11). Therefore, we aim to compare the outcomes of patients with full access to healthcare who self-identified their ethnicity as black or white undergoing RARP in our institution.

Materials and Methods

Study population

We used our Institutional Review Board--approved (number 237998) prospectively maintained database. We included 396 self-identified black patients from 2008 to 2017 and compared to 4929 self-identified white patients operated on during the same period. We considered patients who underwent primary RARP with a minimum follow-up of 5 years. We excluded patients who underwent dialysis, kidney transplant recipients, and salvage RARP after focal therapy or RT, concomitant abdominal pelvic surgery such as hernia repair or appendectomy (black n =26, white n = 340), and cancer status unknown or not available (black n= 29, white n =249).

Propensity Score Matching

Controlling for baseline differences, 341 black patients were propensity score (PS) matched in a 1:1, 1:2. 1:3 ratio from a cohort of 4340 white patients. Using a multiple variable logistic regression model for PS, based on: age, prostate specific antigen (PSA) levels, body mass index (BMI), Charlson comorbidity index (CCI), CCI in 3 groups, Sexual Health Inventory for Men (SHIM) score, American Urological Association symptom score (AUASS), AUASS in 3 groups, prostate specimen weight, PSA density, follow up time, year of RARP, biopsy International Society of Urological Pathology (ISUP) grade group, biopsy primary pattern Gleason score (GS), biopsy secondary pattern GS, biopsy total GS, clinical tumor stage, D'Amico risk classification, smoking history, family history of prostate cancer and breast cancer respectively.

Matching was performed using the nearest-neighbor matching algorithm (caliper width 0.15 of the standard deviation of the logit score) with a 1:1 ratio without replacement (12). The balance diagnostics applied to covariates was standardized mean differences comparing before and after PS matching in the two groups (13).

Statistical Analysis

Using established guidelines (14) continuous variables were reported as median and interquartile range (IQR) and categorical variables as absolute and relative frequencies. A two-sample Wilcoxon rank-sum test was used for testing the hypothesis of equal distributions in the matched groups for continuous variables. The Fisher's exact test compared the groups for categorical variables. For continuous outcomes, the confidence intervals (CIs) for the difference between the two study groups median was performed with Hodges-Lehmann method (15). Cumulative incidence functions (CIF) for post-operative recovery of potency, continence, and biochemical recurrence (BCR) were estimated by the Kaplan-Meier method.

The STSURVDIFF module (16) in Stata was used to estimate the difference of cumulative incidences groups (with CIs) between study groups for time-to-event outcomes at fixed time points after RARP. The statistical analyses were performed using Stata 16 and R version 4.0.2 (Stata Corp., College Station, TX, US). Statistical significance is defined as $p < 0.05$ for a two-tailed test.

Surgical technique

All patients underwent RARP by a single surgeon via a six-port configuration, transperitoneal retropubic approach, using the da Vinci surgical system (Intuitive Surgical, Sunnyvale, CA, USA) with our previously described techniques (17-20). We used athermal retrograde release of neurovascular bundles and posterior reconstruction (12).

Endpoints

Primary endpoints were the comparative Pentafecta for the attainment of continence and potency, BCR, postoperative early complications, and positive surgical margins (PSM) between the groups. Continence is defined as the use of no pads, potency as achieving and maintaining erections sufficient to perform intercourse (with or without phosphodiesterase type 5 inhibitor use), and BCR is defined as a postoperative PSA above 0.2 ng/mL. Additionally, we compared the peri-operative characteristics of the groups.

Secondary endpoints of the study were comparing groups of the time to hormonal, radiotherapy, and chemotherapy, where applicable.

RESULTS

Table-1 demonstrates part of the variables before (341 vs. 4340) and after PS 1:1 matching (341 vs. 341). Median follow-up was 2915 vs. 2917 days or approximately 8 years in both groups. Perioperative findings are presented in Table-2, with similar estimated blood loss (EBL) and median console time for both groups. The median operative time was 5 minutes longer in the black patient group (p=0.02). The maximum hospital stay was 13 days for black patients and 6 days for white patients, with the median time being 1 day in both groups. The complication rates classified by the Clavien-Dindo scale, and 30-day readmission rate did not differ among the groups.

Pathological and cancer status outcomes are described in Table-3. PSM and ECE events were 13.4 % vs 14.4% (p = 0.75) and 23.8% vs 27.3% (p=0.3) respectively. BCR and persistent PSA (or PSA that did not decrease to <0.1ng/mL post RARP) was 13.8% vs 14.1% and 4.4% vs 3.2% respectively (p=0.75).

Figure-1 describes the cumulative incidence function (CIF) for potency recovery between groups (p=0.3). A Cox regression sub-analysis for potency recovery showed a statistically significant difference in white patients if pre-RARP SHIM was >17 (p=0.04), but not if SHIM was ≤17 (p=0.16). Patients with pre-operative SHIM >22 (p=0.4), SHIM ≤22 (p=0.9), age at RARP >65 (p=0.7) or ≤65 (p=0.1) did not have statistically significant differences in potency recovery.

The continence recovery CIF curve (Figure-2) showed a non-significant statistical difference in recovery (p=0.3) overall. Further comparative analysis performed based on age, with patients >65 (p=0.25) and ≤65 years old (p= 0.051) was similar between groups. BCR rates over time was compared in Figure-3 (p=0.9). Only one death for cancer was observed (white patient group), hence cancer specific survival cannot be analyzed in our study.

Table 1 - Comparison of variables for study groups prior to and after 1:1 PS match. IQR (Interquartile range), PS (propensity score), SDD (standardized difference), PSA (prostate specific antigen), BMI (body mass index), CCI (Charlson comorbidity index), SHIM (Sexual Health Inventory for Men), AUASS (American Urological Association symptom score), ISUP (International Society of Urological Pathology).

Variable	Black Patients (N=341)	Before PS matching			After 1:1 PS matching		
		White Patients (n=4340)	P value	SDD	White Patients (n=341)	P value	SDD
Age, years (IQR)	59 (53-63)	62 (56-67)	<0.001	0.41	59 (52-64)	0.99	-0.01
PSA,ng/mL (IQR)	5.3 (4.3-7.8)	5.1 (4-6.9)	0.113	-0.96	5.4 (4.3-7.6)	0.89	0.07
BMI, kg/m^2(IQR)	28.4 (25.9-31.6)	27.6 (254-30.4)	0.005	-0.22	27.8 (25.5-31.2)	0.12	-0.13
CCI score (IQR)	2 (1-2)	2 (1-2)	0.003	0.24	2 (1-2)	1	0.03
CCI, n (%)							
0-1	152 (44.6)	1499 (34.5)	<0.001	-2.1	150 (43.9)	0.5	-0.01
2-3	180 (52.8)	2615 (60.3)		0.15	176 (51.6)		-0.02
≥4	9 (2.6)	226 (5.2)		1.33	15 (4.4)		0.09
SHIM score (IQR)	20 (15-24)	21 (15-25)	0.24	-0.028	22 (16-25)	0.24	0
Prostate weight grams (IQR)	51 (42-62)	48 (40-60)	0.025	-0.12	49 (41-60)	0.54	-0.12
PSA Density	0.10 (0.08-0.15)	0.10 (0.07-0.14)	0.37	-0.05	0.12 (0.08-0.16)	0.14	0.12
AUASS (IQR)	6 (2-11)	7 (3-12)	0.14	0.07	6 (3-11)	0.98	-0.02
Follow up, days (IQR)	2915 (2193-3646)	2925(2222-3647)	0.27	0.11	2917(2249-3309)	0.32	0.03
Biopsy ISUP grade group, n (%)							
Grade group 1	157 (46)	2018 (46.5)	0.6	0.01	166 (48.7)	0.9	0.05
Grade group 2	112 (32.8)	1306 (30.1)		-0.06	110 (32.7)		-0.01
Grade group 3	30 (8.8)	495 (11.4)		0.09	26 (7.6)		-0.04
Grade group 4	28 (8.2)	344 (7.9)		-0.01	28 (8.2)		0

Grade group 5	14 (4.1)	177 (4.1)		-0.001	11 (3.2)		-0.05
Clinical stage, n (%)							
T1a	1 (0.3)	7 (0.2)	0.05	-0.03	0 (0)	0.9	-0.08
T1b	0 (0)	2 (0.1)		0.03	0 (0)		
T1c	284 (83.3)	3358 (77.4)		-0.15	275 (80.7)		-0.07
T2a	41 (12)	706 (16.3)		0.12	51 (14.9)		0.09
T2b	5 (1.5)	150 (3.5)		0.13	5 (1.5)		0
T2c	8 (2.4)	89 (2.1)		-0.02	8 (2.4)		0
T3a	1 (0.3)	25 (0.6)		0.04	1 (0.3)		0
T3b	0 (0)	2 (0.1)		0.03	0 (0)		0
T4	1 (0.3)	1 (0.02)		-0.07	1 (0.3)		
D'Amico Risk, n (%)							
Low	144 (42.2)	1820 (41.9)	0.3	0.01	145 (42.5)	0.75	0.01
Intermediate	137 (40.2)	1871 (43.1)		0.06	143 (41.9)		0.04
High	60 (17.6)	649 (15)		-0.07	53 (15.5)		-0.06
Smoking, n (%)							
No	273 (80.1)	3189 (73.5)	0.001	-0.15	279 (81.8)	0.78	0.05
Yes, former	42 (12.3)	872 (20.1)		0.212	36 (10.6)		-0.06
Yes, current	26 (7.6)	279 (6.4)		-0.05	26 (7.6)		0
Family History CaP, n (%)							
No	202 (59.2)	3793 (87.4)	0.03	0.12	203 (59.5)	1	0.01
Yes	139 (40.8)	547 (12.6)		-0.12	138 (40.5)		-0.01
Family History Breast Ca, n (%)							
No	308 (90.3)	3793 (87.4)	0.12	-0.93	290 (85)	0.05	-0.16
Yes	33 (9.7)	547 (12.6)		0.09	51 (15)		0.16

Table 2 - Peri-operative outcomes for study groups, 1:1 PS match. EBL (estimated blood loss), IQR (Interquartile range), PS (propensity score).

Perioperative	Black Patients (N=341)	After 1:1 PS matching	
		White Patients (n=341)	P value
EBL mL, (IQR)	100 (75-150)	100 (100-150)	0.83
Operative time, minutes (IQR)	123 (110-138)	119 (106-133)	0.02
Console time, minutes (IQR)	75 (75-80)	75 (75-80)	0.15
In-hospital stay, days, n (IQR)	1 (1-1)	1 (1-1)	0.06
Clavien Dindo, n (%)			
0	314 (92)	323 (94.7)	0.4
1	9 (2.6)	8 (2.4)	
2	15 (4.4)	7 (2.1)	
3	1 (0.3)	2 (0.6)	
4	2 (0.6)	1 (0.3)	
Readmission <30 days, n (%)	5 (1.47)	4 (1.17)	0.5

The overall potency and continence recovery at 12 months was 52% vs 58% (p=0.3) and 82% vs 89% (p=0.3) respectively. In Table-4, the potency and continence recovery, along with BCR, are demonstrated at set time points with cumulative rates for each group. The groups' cumulative rate differences with associated CI for each time point are shown.

DISCUSSION

Literature has cited black ethnicity as a prognostic factor for adverse pathological features and higher PSM rates compared to matched white patients (21, 22). However, the wider utilization of PSA, patient awareness, and acceptance of screening for CaP contributed to a stage shift. The BCR-free survival gap has narrowed between these two ethnic groups in the US (23). Riviere et al. (24) showed from a VA database of 20 million veterans that 60,000 black and white men with equal access to care experienced similar outcomes. However, on the other side, a literature review (25) of men of African descent found CaP data from the Caribbean and the UK differed from the US. The UK's initiative of the National CaP Audit can now assess the impact of universal access from the National Health Service (NHS) on the outcomes of RP according to ethnicity. Furthermore, in some countries, COVID-19 negatively impacted on increasing advanced CaP presentations and a reduction in RP and RT by 26.9% and 14.1%, respectively (26).

Our study investigated the results of a high-volume center and a single surgeon with expertise in RARP among patients who self-identified as black and white ethnicity. Although our institute receives referrals of patients post-Focal and Radiation therapy for Salvage RARP, they were excluded due to significantly variable and generally inferior outcomes compared to primary surgery (27). Further exclusions were abdominal and pelvic surgery due to the potential impact on perioperative and nerve-sparing results (28). Given the high number of white patients in our databank, we were able to consider numerous va-

Table 3 - Pathological and Oncological outcomes for study groups in 1:1 PS match. IQR (Interquartile range), PS (propensity score), PSM (positive surgical margin), ECE (extracapsular extension), BCR (biochemical recurrence), ISUP (International Society of Urological Pathology).

Cancer outcome	Black Patients (N=341)	After 1:1 PS matching	
		White Patients (n=341)	P value
ISUP grade group, n (%)			
1	88 (27.6)	100 (29.3)	0.4
2	160 (46.9)	160 (46.9)	
3	65 (19.1)	53 (15.5)	
4	8 (2.4)	13 (3.8)	
5	20 (5.9)	15 (4.4)	
Tumor upgrade, n (%)			
Yes	145 (42.5)	148 (43.4)	0.8
No	196 (57.5)	193 (56.6)	
PSM, mm (IQR)	2 (1-3)	2 (1-3)	0.9
PSM present, n (%)	46 (13.5)	49 (14.4)	0.8
ECE, mm (IQR)	1 (1-2)	1 (1-2)	0.9
ECE present, n (%)	81 (23.8)	93 (27.3)	0.3
Tumor volume % (IQR)	15 (10-20)	15 (8-20)	0.4
Pathological Stage, n (%)			
≤T2c	50 (14.6)	64 (18.7)	0.4
T3a	2 (0.6)	1 (0.39)	
T3b	229 (67.2)	210 (61.6)	
T4	60 (17.6)	66 (19.4)	
Positive lymph node, n (IQR)	0 (0-0)	0 (0-0)	0.6
Cancer Status, n (%)			
BCR	47 (13.8)	48 (14.1)	0.75
Persistent PSA	15 (4.4)	11 (3.2)	

riables on the PS to improve the precision (29) and balance between the groups (30) before the analysis. It is known that family history and the association with the BRCA2 gene increase the risk of CaP (31). However, we could not consider these variables in the PS due to the reduced number of patients.

Regarding our comparative functional outcomes, we observed in Table-4 that the cumulative risk showed a rapid potency recovery in the first year after RARP, although not statistically significant between the groups. DeCastro et al. (32) analyzed their single center results in the first-year post RARP between black and non-black patients

Figure 1 - CIF of potency recovery for both groups in 1:1 PS match, P=0.3.

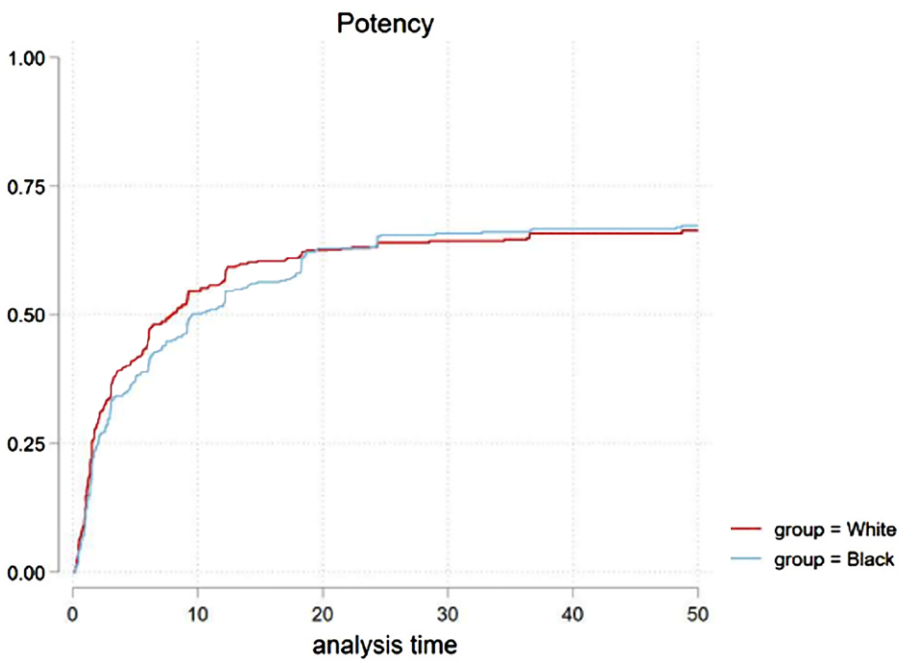


Figure 2 - CIF of continence recovery for both groups in 1:1 PS match, P=0.3.

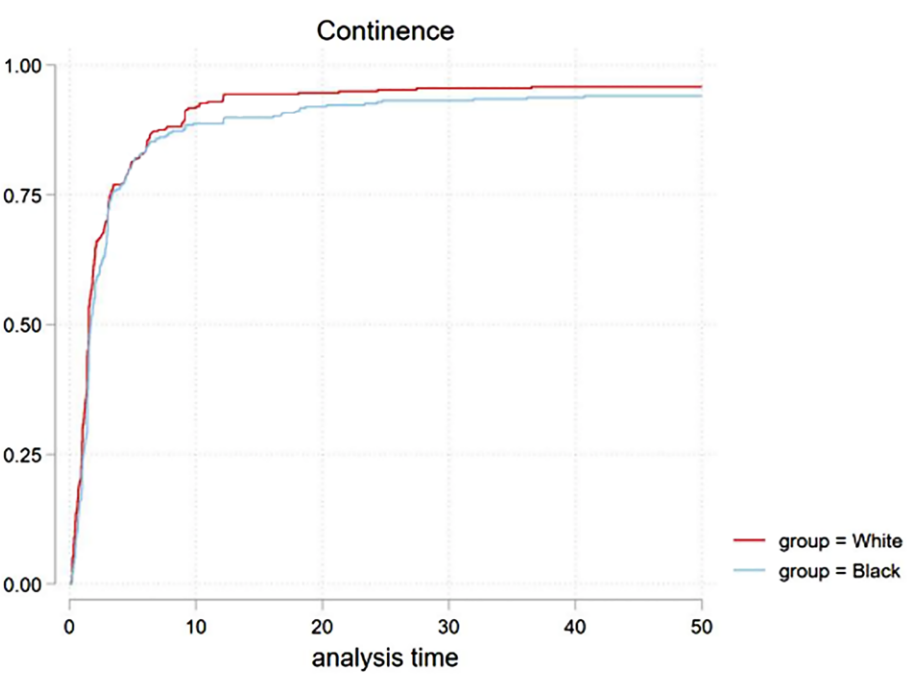
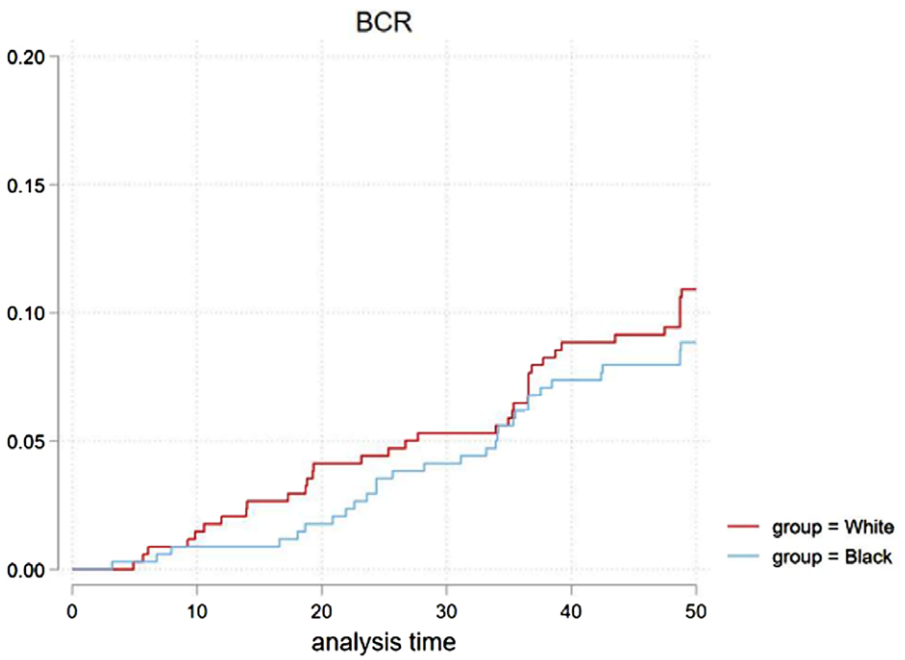


Figure 3 - CIF for BCR for both groups in 1:1 PS match, P=0.9.



and found equivalency in both potency and continence at 6 months but inferior outcomes in black patients at 12 months. Another study attributed anatomical differences, such as median urethral length in Asian compared to non-Asian patients (33), to differences in Expanded Prostate Cancer Index Composite for Clinical Practice (EPIC-CP) urinary scores post-RP. Furthermore, Von Bodman et al. (34) compared MRI scans among ethnic groups to reveal a steeper symphysis pubis angle and mid-pelvic area in black patients. Despite these findings in previous studies, we found surgical outcomes equivalence between groups, including PSM rates, due to our standard surgical technique respecting anatomical landmarks. Meticulous surgical care must involve technique adaptability according to the tumor burden and biopsy histology (35).

Our patients with biopsy ISUP 1, who elected RP overactive surveillance, made up the majority of the cohort. A previous study from John Hopkins (36) found that black men with very low-risk CaP who underwent RP had disease upgrades and higher rates of PSM compared to other ethnic groups. This study suggested counseling black patients on their oncologic risks around treatment options. Individual cancer referral centers' results vary based on practice parameters such as volume and individual surgeon experience. Our study could not demonstrate a clinically or statistically difference in tumor upgrades, PSM, and BCR between groups, suggesting that the oncologic outcomes are comparable in our expertise. BCR as a stand-alone (Figure-3) or with persistent PSA (Table-3) presented a statistically non-significant difference. This is also reported by a multicentric study (37) assessing ISUP 4 and 5 CaP, which concluded no difference in the rate of adverse oncologic outcomes by ethnicity.

The overall survival and cancer-specific survival were not analyzed due to the low event rate in our study. Data from the American College of Surgeons National Surgical Quality Improvement Program included 38,642 patients (38) undergoing major urological cancer surgery (RP, radical/partial nephrectomy [PN/RN], and radical cystectomy [RC]). It analyzed trends based on ethnicity and found no increase in the risk of 30-day postoperative complications between groups. After controlling for comorbidities, black ethnicity

Table 4 - Time to event Functional and BCR outcomes for study groups in 1:1 PS match. CI = confidence interval, HR=hazard ratio versus black patients as reference. s

Outcome	Cumulative rate (%)		Difference, % (95% CI) *	HR (95% CI)	P value**
	Black Patients (N=341)	White Patients (n=341)			
Potency, months					
3 months	31	39	7.7 (0.6 – 14.9)	0.9 (0.7 – 1.1)	0.3
6 months	39	47	7.2 (-3 – 14.6)		
9 months	46	54	8.4 (0.9 – 15.9)		
12 months	52	58	6.3 (-1.1 – 13.8)		
24 months	63	67	3.4 (3.7 – 10.6)		
36 months	66	68	1.4 (-5.7 – 8.4)		
Continence					
3 months	68	69	1.8 (-5.1 – 8.6)	0.9 (08 – 1.1)	0.3
6 months	83	84	-0.3 (-5.8 – 5.2)		
9 months	88	90	2.9 (-1.7 – 6.6)		
12 months	89	92	2.3 (-1.9 - 6.6)		
24 months	93	94	1.2(-2.5 – 4.9)		
36 months	94	94	0.6 (-2.9 – 4.1)		
BCR					
3 months	0	0	-0.3 (-0.9 – 0.3)	0.9 (0.7 – 1.5)	0.9
6 months	0.3	0.6	0 (11.1 – 1.1)		
9 months	0.9	0.9	0.3 (-1.2 – 1.8)		
12 months	0.9	1	0.9 (-0.8 – 2.6)		
24 months	3	4	0 (-2.8 – 2.8)		
36 months	6	5	-2.1 (-5.5 – 1.4)		

* Difference as white – black

** Long-rank test to compare cumulative incidence functions.

did not show independent association for complications in RP (odds ratio [OR] = 1.08, 95% CI: 0.92-1.29). Our results were also compatible with these findings and could not find differences between the groups in EBL, Clavien-Dindo complications, and readmission rates.

The oncological outcomes in a universal healthcare institution in the US have been previously found to be superior or similar as it eliminated access to healthcare barriers. Our referral center accepts privately insured, universally insured Medicare, US Veterans Affairs (VA) populations, and international patients. In our experience, we believe that this full healthcare access is crucial to minimize the difference in outcomes, similar to findings in a universal healthcare (8,

20), or single payer systems (10) due to appropriate prostate cancer screening with PSA, access to imaging exams such as Multiparametric Resonance Image (MRI), and follow-up according to established guidelines.

Despite its strengths, this study is limited by its retrospective design and all inherent risks of bias. Additionally, an absence of analysis from other ethnic cohorts and the unmeasured variation in self-identifying as white and black. Furthermore, this series reflects optimal outcomes of a high-volume expert single surgeon, and these results may not be reproducible in low-volume centers. However, to our knowledge, this is one of the largest cohorts in the literature comparing outcomes in patients from two ethnic groups with similar peri-operative characteristics (balanced with PS) and full access to gold-standard treatments for prostate cancer.

CONCLUSIONS

In our study, comparing two ethnic groups with similar preoperative characteristics and full access to screening and treatment showed compatible RARP results. We could not demonstrate outcomes superiority in one group over the other. However, this data adds to the growing body of evidence that the racial disparity gap in prostate cancer outcomes can be narrowed if patients have appropriate access to prostate cancer management. It also could be used in counseling surgeons and patients on the surgical intervention and prognosis of prostate cancer in patients with full access to gold-standard screening and treatment.

CONFLICT OF INTEREST

None declared.

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SURGICAL TECHNIQUE

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Reproducibility of a modified posterior reconstruction during robotic intracorporeal neobladder reconfiguration

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ABSTRACT

Objective: Robotic intracorporeal neobladder reconstruction is a complex procedure in which the approximation of the reservoir to the urethral stump can be a demanding step.
The aim of the study is to evaluate the reproducibility of a modified posterior reconstruction (PR) during the reconfiguration of intracorporeal neobladder after robot assisted radical cystectomy (RARC).
Materials and Methods: From July 2021 to July 2022, 35 RARC were performed, and 17 patients underwent intracorporeal neobladder reconstruction. A PR was planned in males (14). Intra- and peri-operative data were collected.
Surgical technique: RARC and node dissection are performed. Afterwards, 40-cm ileal segment is isolated; the portion with the more adequate mesenteric length is brought down to the pelvis. A modified PR is performed with a double-armed barbed suture: a first layer connects the Denonvillier's fascia to the rhabdosphincter in a running fashion; the second layer is created with the other arm and approximates the posterior side of the ileal segment towards the urethral stump. In the anterior caudal part of the ileum, a 1.5-cm incision is made to realize the neobladder neck; the neovesical--urethral anastomosis is performed with a second bidirectional suture.
Results: Anastomotic and PR time were 14 (range 7-20) and 5 minutes (4-8), respectively. A single Clavien IIIa complication was recorded in a patient who underwent NAC and had a *C. albicans* superinfection in the post-operative course. All patients were discharged with complete or acceptable bladder voiding. Twelve patients with follow--up >90-days reported a satisfying daytime continence.
Conclusions: PR represents a simple technical refinement that improves neobladder--urethral anastomosis by favoring ileal approximation to the urethral stump and decreasing anastomotic tension.

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INTRODUCTION

Radical cystectomy (RC) is the mainstay of treatment of bladder cancer (1, 2). Even if bladder sparing strategies are challenging the role of surgery (1, 3), technical and technological advances are making the surgical procedure less invasive. RC is a complex procedure that may involve the combined surgery of the urinary and gastrointestinal tract (4-6). It can be performed either open, laparoscopically and robotically; current EAU Guidelines suggest that no approach is over another. Robot-assisted radical cystectomy (RARC) with intracorporeal neobladder have been recently recognized as an approach able to preserve global health related quality of life (7, 8); however, it has been the slowest adopted since challenging and time-consuming (9). To simplify the reconstruction of reservoir, several technical refinements have been described (9-12). One of the most challenging parts of robotic intracorporeal neobladder reconstruction is the approximation of the ileal segment to the urethral stump. Some tricks were developed to this purpose, such as decreasing the Trendelenburg or the use of vessel loops around the bowel to maximize intestinal brought down (13).

A modified posterior reconstruction (PR) was proposed as well, to facilitate neobladder-urethral anastomosis and enhance urinary continence recovery (13). The technique has been used with a modified Studer neobladder (13): the double-layer suture approximates the Denonvillier's fascia to the rhabdosphincter and then connects the posterior site of neobladder neck to urethral stump before the anastomosis.

The current paper aims to determine whether the approach is easily reproducible with other reconfigurations; to this purpose, a PR during a modified Y-shaped neobladder reconstruction was evaluated in male patients.

MATERIALS AND METHODS

Between July 2021 and July 2022, 35 patients underwent RARC for high-grade and/or muscle-invasive bladder cancer. The study aims to evaluate the feasibility and reproducibility of a PR in the setting of neobladder reconstruction; inclusion criteria were patients aged 18-80, male gender, undergoing orthotopic diversion. Outcome measures were anastomotic and PR time; intra- and post-operative complications were recorded as well. The removal of the trans-urethral catheter was planned between PO Day 12 and 16. All procedures were performed by a single surgeon (BR) highly expert in robotic pelvic and reconstructive surgery. Follow up was recorded at 30-days, 3, 6, 12 months.

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A full video of the technique is available at https://youtu.be/PyZ8nGOmd2Y .

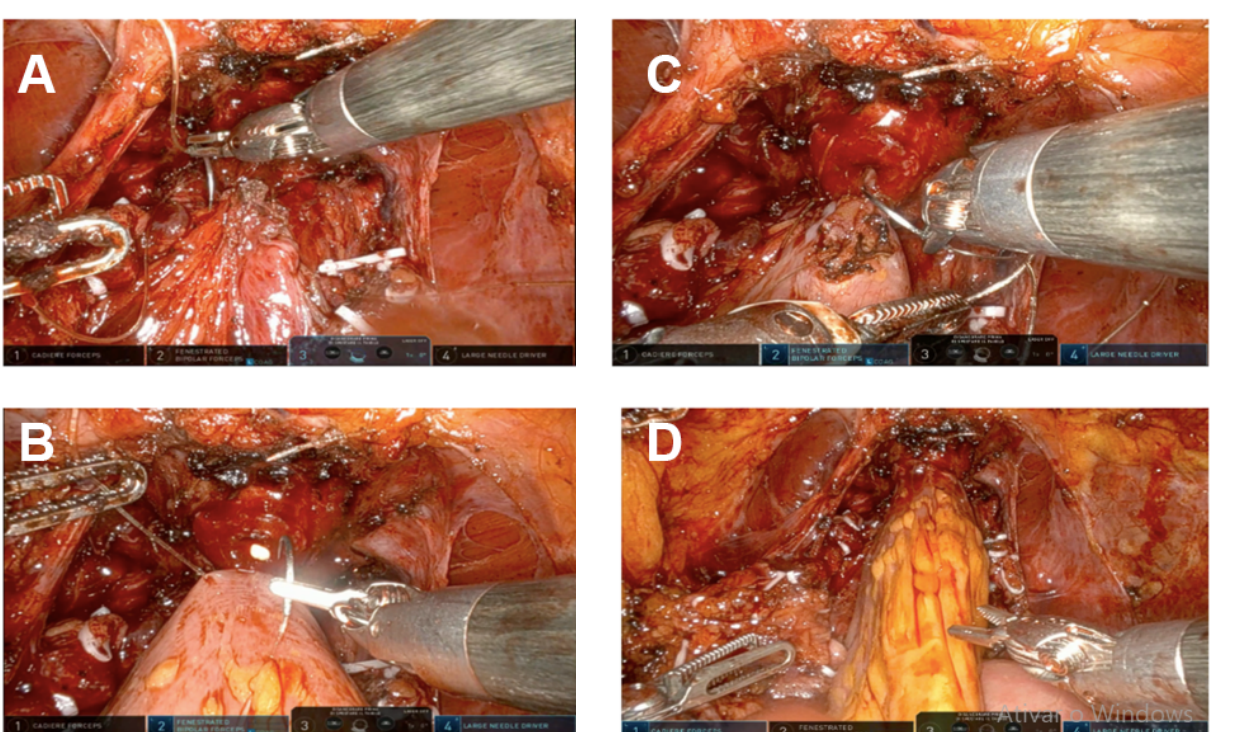
An open supra-umbilical access is performed with the placement of an Alexis device. The other robotic ports and those for the assistant are created according to the Asimakipoulos and Gaston description (14). The procedure starts with the identification and isolation of ureters bilaterally from above iliac vessels until bladder insertion. At bladder level the ureter is closed with median size Hem-o-lok and then sectioned. In males, the peritoneum at seminal vesicle level is incised and the plane between Denonvilliers' fascia and the posterior face of the prostate is developed (between bladder and vagina in females). Lateral aspects of the bladder are developed bilaterally, and vesical pedicles are clipped and transected. Inverse U peritonectomy is carried out between the two internal inguinal rings, umbilical arteries are transected and access to the Retzius space is created. In males, the preservation of neurovascular bundle is performed when recommended, with a high anterior release of the peri-prostatic nerves. The anterior aspect of the bladder is developed, and the Santorini complex is severed and then sutured. The urethra is isolated and incised after a large hem-o-lok is placed to prevent urine spillage. The urethral stump is maintained as long as possible. Frozen sections of distal ureters and urethra are performed, meanwhile, an extended pelvic nodal dissection is carried out bilaterally.

Afterwards, a 40-50 cm ileal segment is isolated; the portion with the more adequate mesenteric length is chosen to be brought down to

the pelvis. The reconfiguration of the neobladder starts from the posterior reconstruction and vesico-urethral anastomosis. The median part of the isolated ileal segment is pushed towards the urethral stump. A modified PR is performed with a double-armed barbed suture (Stratafix3–0, Ethicon™) used as a running suture. The first layer connects the Denonvillier's fascia and the rhabdosphincter (Figure-1A), whereas the second layer approximates the posterior side of the ileal segment towards the urethral stump, by using the other side of the double armed suture (Figure-1B). While tying the suture, caudal approximation of the ileum is supported by the assistant and by the fourth arm. In the anterior caudal part of the ileal loop, a 1.5-cm incision is made with robotic scissor to realize the neobladder neck; the neovesical-urethral anastomosis is performed with a second 3-0 Stratafix bidirectional needle (Figure-1C). Figure-1D depicts the final view of the ileo-urethral anastomosis. A schematic drawing is provided in Figure-2.

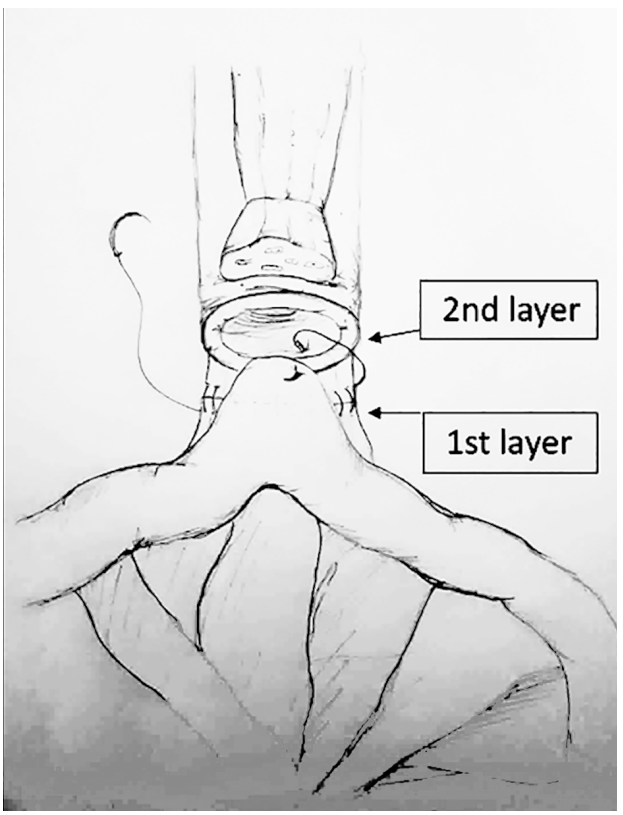
The isolation of the segment is made cranially on each side by using a mechanical laparoscopic stapler; ileal-ileal anastomosis is performed thereafter. The reverse tubular U-segment of the ileum is configured, and the ileum is detubularized. The reconfiguration of the neobladder starts from the suture of the posterior plane with a 3/0 running barbed suture (3-0 barbed suture); the cranial part is folded downwards and anastomized with the bladder neck. The lateral horns of the reservoir are closed in their anterior aspect with a 3-0 running suture. The neobladder it tested for leakage; then uretero-neobladder anastomosis is performed with a direct anastomosis of each spatulated ureter in the dorsal part of the horns (4-0 polydioxanone). Ureteral stents are placed before suturing the anterior plate and are brought out through the anterior abdominal wall.

Figure 1 - Intra-operative images of PR



A) First layer of the modified PR; connection between the Denonvillier's fascia and the rhabdomiosphincter; B) Second layer of the modified PR, that involves the ileal segment brought down to the pelvis; C) Anterior opening of the ileum with robotic scissors, for the realization of the anastomosis; D) the anastomosis is completed

Figure 2 - Drawing depicting the two layers of posterior reconstruction during intra-corporeal neobladder reconstruction. Layer 1: the more posterior, connection between the Denonvillier's fascia and the posterior rhabdomiosphincter; Layer 2: connection between the ileum and the urethral stump



RESULTS

Seventeen out of 35 patients underwent an intracorporeal neobladder reconfiguration. The series consisted of 14 males and 3 females; the latter were pre-operatively counseled with the gynecologist for a sexual sparing approach. All male patients received a PR associated to the neobladder-urethral anastomosis. A detailed description of patients who underwent neobladder reconstruction with PR is provided in Table-1.

Anastomotic and PR time were 14 (range 7-20) and 5 minutes (4-8), respectively. No intra-operative complications were recorded. Post-operative course was uneventful in all patients except two cases of neobladder leakage (one of them requiring nephrostomy tube placement) and a single case of persistent hematuria due to inadvertent catheter dislodgement. The patient who underwent nephrostomy drainage had received a prior neoadjuvant chemotherapy and was affected by a *C. albicans* urinary superinfection. In the absence of leakage, the neobladder-urethral catheter was removed within PO Day 12 and 16. All patients were discharged with ultrasonographic confirmation of complete or acceptable bladder voiding (< 50-100 mL). A single patient was re-admitted within 30 days due to febrile UTI. Currently, 12 male patients have > 90-day follow up (range 3-12 months); all of them report a satisfactory daytime continence (no pad use for 10 patients and 0/1 pad/day for 2 patients) and a mild degree of a nighttime incontinence (use of 1 pad/night).

DISCUSSION

A posterior reconstruction with the involvement of the ileal loop within the second layer is an easy and reproducible step of robotic intracorporeal neobladder reconstruction.

Recently, Checcucci et al. described a RARC series with a simple posterior reconstruction, which includes the Denonvillier's fascia and a peritoneal flap from the Douglas pouch: unlike our procedure, the technique fails to comprise the ileal loop within the reconstruction (15).

A modified PR incorporating the ileal segment has been previously described in a series of robotic Studer neobladder performed at the Karolinska University Hospital (13). Authors found that the technique could be easily performed intracorporeally with a negligible additional console time; furthermore, a 100% and 44% daytime and nighttime continence at 12-months were recorded, though the small series and the absence of a control group precluded any conclusion to this point.

A posterior reconstruction has been long used during radical prostatectomy. Since its first description in 2006 (16), the technique gradually spread and has been successfully adapted to minimally invasive surgery. Its benefit on early urinary continence recovery after radical prostatectomy has been reported in a Cochrane review by Rosemberg et al. (17) and another meta-analysis (18).

Table 1 - Full descriptive analysis of demographics, clinical and pathological data of patients undergoing neobladder reconstruction.

Age	Mean ? SD (range)	64.5 years ? 7.5 (48-75) years
Gender	Female (%)	3 (17.6%)
	Male (%)	14 (82.4%)
BMI	Mean ? SD (range)	27, ? 1.4 (22.1-31.7)
Smoker	Yes (%)	7 (41.2%)
	No (%)	6 (35.3%)
	Previous (within 5 years)	4 (23.5%)
Histological examination (after TURBT)	T1 high/very high risk (%)	5 (29.4%)
	T2 (%)	9 (53%)
	Recurrent/multifocal CIS (%)	3 (17.6%)
Previous BCG therapy	Yes (%)	4 (23.5%)
	No (%)	13 (76.5%)
Neoadjuvant CHT	Yes (%)	4 (23.5%)
	No (%)	13 (76.5%)
Anastomotic time	Mean (range)	14 (7-20) minutes
PR time	Mean (range)	5 (4-8) minutes
Intra-operative complications	Yes (%)	0 (0%)
	No (%)	17 (100%)
Post-operative complications	Yes (%)	3 (17.6%)
	No (%)	14 (82.4%)
30-days readmission	Yes (%)	1 (5.9%)
	No (%)	16 (94.1%)
Histologic stage: T (tumor)	T0	3 (17.6%)
	Ta	0 (0%)
	Tis	3 (17.6%)
	T1	1 (5.9%)
	T2	6 (35.3%)
	T3	2 (11.8%)
	T4	2 (11.8%)
Histologic stage: N (lymph nodes)	N0	12 (70.6%)
	N1	4 (23.5%)
	N2	1 (5.9%)
	N3	0 (0%)
Histologic grade	LG	3 (17.6%)
	HG	14 (82.4%)
Histological stage: R (surgical margins)	R0	17 (100%)
	R+	0 (0%)

Actually, after the disruption occurring during pelvic surgery, PR restores the anatomical and functional length of the rhabdosphincter and reestablish the continuity of the musculofascial plate. Beyond the use for continence recovery, PR may represent a support for anastomosis, by reducing the tension and improving the approximation between the bladder neck and urethral stump.

The same advantages apply to the neobladder-urethral anastomosis after RARC.

Unlike open surgery, the first step of most robotic intracorporeal neobladder is the ileo-urethral anastomosis performed prior to the detubularization and reconfiguration of the ileum itself. Some tricks enable the approximation of the ileal segment to the pelvis, such as the use of two vessel loops passed around the intestine through the mesentery to facilitate the traction toward the urethra. However, the ileum wall has a soft tissue texture that can be damaged by instruments tractions, especially in case of inadvertent conflicts, or by the tension itself. A modified posterior reconstruction prior to the anastomosis may facilitate the approximation of the ileum toward the urethral stump and reduce the tension on the bowel wall. The posterior support to the anastomosis provides advantages also for catheter placement, especially in cases of difficult unaligned bladder neck.

The modified PR appears not to impair operative time. Overall, the procedure takes approximately 6 minutes, similar to the length reported in the series with Studer diversion.

The limitation of the current study is the small sample size and the absence of a control group. Thus, any consideration about urinary continence is precluded. Nevertheless, the primary endpoint of the study was to test the *reproducibility* of the PR rather than to prove its effectiveness to improve continence recovery.

In conclusion, a PR that involves the Denonvillier's fascia, the posterior site of neobladder neck and the rhabdosphincter is a simple and reproducible step that may maximize the approximation of the reservoir toward the pelvis, reduce anastomotic tension and simplify robotic intracorporeal reconstruction of orthotopic neobladder.

CONFLICT OF INTEREST

None declared.

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EXPERT OPINION

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Will the advances in retrograde intrarenal surgery extinguish percutaneous nephrolithotomy for stones larger than 2 cm?

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COMMENT

Since 1976, when percutaneous nephrolithotomy (PCNL) was first described (1), it has been an excellent choice of endourological treatment for large renal stones. In fact, both American Urological Association (AUA) and European Association of Urology (EAU) guidelines currently consider PCNL the preferred surgical approach to stones larger than 2 cm (2, 3). However, recent technological advances in retrograde intrarenal surgery (RIRS) including development of digital ureteroscopes and high-power lithotripsy generators result in better stone free rates (SFR) while offering less morbidity to patients, hence broadening the indications of this technique, including large and complex stones (4, 5). Better outcomes translate into an increasing number of RIRS worldwide (6), but bring about the question: will RIRS, ultimately, extinguish PCNL as the main surgical treatment for large stones?

The key gamechangers related to RIRS evolution include the development of disposable ureteroscopes and the new Thulium fiber laser (TFL). Single-use devices offer some advantages over the reusable flexible ureteroscopes: they are lighter (which may prevent fatigue in long lasting cases especially when treating large burden stones), offer a better deflection angle and provide superior image quality (7). Other authors also observed single-use device was associated with shorter operative time and higher stone free rates with possibly less complications (8-10). Moreover, the use of disposable material may reduce total costs to the health care system, which is vital within developing countries perspectives, including Brazil (7). Current literature on TFL provides compelling results when compared to Holmium laser, indicating it is a milestone in RIRS: higher stone ablation rate (2 to 4 times faster), less calculi retropulsion and more efficient fragmentation generating smaller fragments. The possibility of using laser fibers as thin as 150 micrometers can provide better scope deflection (11) and could allow for future further instruments miniaturization (12-14).

Nevertheless, complications associated with RIRS cannot be underestimated – not only because of its continuously increasing use but also because of their potential severity (15). Ureteral access sheath (UAS) facilitates fragment basketing if the surgeon opts for stone fragmentation and provides a better irrigating flow – which is essential for better visualization and maintenance of pelvicalyceal temperature and low pressure and therefore might play an active role in the procedure success (16-18). However, Traxer et al. reported on an overall incidence of UAS related ureteral lesions of 46.5%, of which 13.3% were classified as

severe (19). This can develop into both short (such as hematuria and the need of ureteral stent for an extensive period) and long-term complications (such as ureteral stenosis) and should be avoided.

Furthermore, a recent publication showed that UAS increased the odds of a post-operative emergency department visit and re-hospitalization, without better SFR (18). Unusual but dramatic complications related to the UAS have been described, such as the entrapment of a flexible ureteroscope (fURS) inside the sheath due to a breakage of the outer surface of the scope caused by excessive manipulation (20).

Rise in intra-renal temperature during stone fragmentation is another concern in RIRS, and it is related to high laser power (21), prolonged time of pedal activation and irrigation pressure. They may implicate in fluid heating and thermal dose exposition (22). An in vitro model with UAS and common Holmium laser settings verified high temperatures can result after as little as 1 second of laser activation especially at power settings over 10 W (23).

Another key aspect of RIRS procedure is the use of ureteral double J stents before or following the procedure. A meta-analysis from Chang et al. concluded that pre-stenting may improve stone free rates in fURS for large kidney stones, with no difference in complication rate (24).

A study that analyzed almost 10,000 ureteroscopies, observed 73% of ureteral stenting following surgery. Pre-stented status, age, stone size and location were associated with stent use after surgery. Stent usage significantly increased the odds of an unplanned emergency hospital visit after surgery (25).

Also, "forgotten stent" can develop into severe encrustation (26) and its removal may require refined management planning and advanced surgical techniques (27, 28). Strategies to prevent such problem include stent judicious use and the implementation of modern technology to keep track of stented patients (29, 30).

There are potentially life-threatening complications in RIRS even in experienced endourologists hands (31). A systematic review showed an incidence of 0.45% of post RIRS perirenal hematoma with a mean stone size of 1.7 cm, and in which 17.5% of the patients needed surgical intervention – resulting eventually in nephrectomy and even death (4).

Furthermore, longer surgical time had a significant association with systemic inflammatory response syndrome (SIRS) and urosepsis after fURS, which occurred in 6.9% and 5.0%, respectively, among over 8.000 studied patients (32, 33). Other reports reported on a rise in RIRS-related deaths over the past decade, associating high stone burden as predictive factor for worse results, requiring an effort to reduce operative time with staged procedures if needed in order to decrease morbidity, rehospitalization, and mortality following ureteroscopies (15, 34).

Residual fragments after RIRS also merits attention. Sur et al. reported on 20-43% of residual fragments are associated with stone events including pain and emergency department visits, reinterventions, and even calculi regrowth (35). A series of fURS comprising more than 400 patients with stones larger than 2 cm revealed a cumulative SFR of 85% (36). However, in nearly all cases, plain abdominal radiograph and/or renal ultrasound were used to assess residual fragments, possibly leading to an over-estimation of the clearance result. Indeed, when using computerized tomography (CT) to determine SFR, results are less than satisfying. Studies which performed abdominal CT scan up to 3 months after initial RIRS showed visible residual fragments varying from 38 to 50% of the procedures (37, 38). Portis et al. prospectively evaluated patients with renal calculi up to 15 mm, and even after a special effort to clear all stones in fURS (by using ureteral sheaths, breaking the stones in upper pole and actively retrieving all fragments), achieved a complete removal status by CT criteria in only 54% of cases (39).

One could argue that residual fragments smaller than 4 mm are less likely to experience post-operative stone growth, complications or require reintervention (5). Rebuck et al. reported a 19.5% chance of experiencing a calculus related event (such as emergency visit, hospitalization or surgery) after RIRS in patients with post-operatory fragments up to 4 mm by CT measurement (40). In fact, according to a review about the natural history of asymptomatic residual stone after this

procedure, there was a 44% chance of a stone related event: re-intervention was predictable based on fragment size (p=0.017), calculi < 4 mm led to 18% re-operation (vs. 38% in > 4 mm), and even residual stones > 2 mm were significantly likely to grow (41).

On the other hand, not only RIRS has evolved, but PCNL has also been fighting its way to remain an attractive option for treating large stones. In fact, when analyzing stone procedures, while the proportion of PCNLs has remained fairly stable over the last years, the number of urologists performing their own percutaneous access instead of delegating it to an interventional radiologist has increased substantially (42). Moreover, there are accumulating publications on the development and advantages of ultrasound-guided renal puncture which reinforces the interest of the scientific community on this (43). Ultrasound may offer significant clinical gains for PCNL execution. Lin et al. described identification of a fused renal pyramid by US and doppler use to identify ectopic blood vessels in order to reduce bleeding during calycinal access in percutaneous surgery (44). Moreover, US guidance provides visualization of adjacent viscera, delineation of anterior and posterior calyces, reduction of radiation exposure, real-time imaging of renal parenchyma and detection of radiolucent stones (45).

But perhaps, the most notorious evolution in standard PCNL was the significant shift to miniaturized PCNL (mini-PCNL) allowing reduced parenchymal renal injury. This technique offers a midway option between conventional PCNL and less invasive endoscopic procedures such as RIRS and implicates in using a tract smaller than 22F (46). The reusable equipment and the vacuum cleaner "vortex" effect make mini PCNL more affordable than standard PCNL. Dilation can be performed either in one-shot or with a progressive technique; and the possibility to enlarge from a small to a thicker tract if needed (Matrioska technique) presents mini-PCNL as a very versatile strategy, suitable for the treatment of almost any stone, including those larger than 2 cm (47). When comparing bleeding, a prospective randomized controlled trial reported that mini-PCNL had a significantly lower drop in hematocrit level versus standard PCNL (p=0.02) and less pain at 6 and 24 hours after surgery (48).

Research in new technologies aiming to improve PCNL outcomes continue to blossom. While the high-power lasers can also be used in percutaneous procedures, other lithotripters specific for this surgery have been created. A prospective comparative study of mini-PCNL using Trilogy lithotripter versus TFL in renal stones with a mean size > 2 cm showed that Trilogy achieved significantly better stone fragmentation rate (49). Regarding better learning of renal anatomy and PCNL technique, Parkhomenko et al. described the use of an immersive virtual reality renal model (50). Likewise, Keyu et al. developed a "3D printing personalized percutaneous nephrolithotomy guide plate for PCNL" which allowed for reduced intra-operative blood loss and bleeding related complications (51).

Less aggressive percutaneous procedures led to the proposal of day-hospital discharge. A systematic review from the European Society observed that, for selected patients, standard PCNL is safe and efficient with a low rate of complications or readmissions (52). A propensity score-matching study evaluating day-cases versus inpatient mini-PCNL concluded that the same day discharge PCNL was more cost-effective, with no significant difference in complications along with very low unplanned readmission during the postoperative period of 14 days (53). And a multi-institutional experience compared micro-PCNL in a group of patients who also had same-day discharge versus an inpatient group and reported on equivalent SFR and complication rate (54).

Finally, it is known that RIRS by itself does not offer full access to reach all renal calculi, especially those in lower calyx with long and narrow infundibulum (55). Karim et al. published a systematic review where they concluded that steep infundibular pelvic angle (IPA) (< 30°) seems to be the most important predictor for failure in the treatment of lower pole stones using RIRS, followed by operative time duration and large calculi burden (56). Inoue et al. also showed that an IPA <30° was the only negative risk factor for stone clearance after flexible ureteroscopy for large renal stones (>15 mm) according to their multiva-

riate analysis (57). Tastemur et al. observed that stone size and IPA (< 42.6°) were independent risk factors for success of RIRS procedure (58).

Ozimek et al. analyzed almost 400 RIRS and reported on that steep IPA could be considered the first risk factor predictor for both flexible ureteroscope damage and significant unfavorable postoperative course – occurrence of complications Clavien-Dindo 2 as well as prolonged hospital stay (59). A meta-analysis comparing mini--PCNL and RIRS for the treatment of lower pole stones up to 2 cm reported similar operative and fluoroscopy times, complication rates and length of hospital stay, although mini-PCNL was significantly superior in terms of success rate (60). A recent publication proposed a scoring system based on pre-operative exams and SFR for better selection of endoscopic treatment for lower pole renal stones. A score was given after analyzing the IPA and stone number and diameter, and infundibular length and width, ultimately providing guidance for urologists to decide upon retrograde or percutaneous access (61).

Overall, systematic reviews and meta--analysis comparing directly RIRS and PCNL for renal stones > 2 cm suggest balancing risks and benefits and tailor an individual treatment strategy in a patient-doctor sharing decision (62, 63). Also, previous standard percutaneous nephrolithotomy might impair retrograde intrarenal surgery outcomes (64). However, not only the RIRS and PCNL are not to be seen as competitors, but possibly as complementary - so that endoscopically combined intrarenal surgery (ECIRS) has opportunistically emerged and set its place as another gamechanger. PCNL (and its miniaturizations) will definitely not be extinguished, as both retrograde and percutaneous accesses keep evolving and safer and more efficient procedures develop.

CONFLICT OF INTEREST

None declared.

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UPDATE IN UROLOGY

MALE HEALTH

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Editorial Comment: Secondary polycythemia in men receiving testosterone therapy increases risk of major adverse cardiovascular events and venous thromboembolism in the first year of therapy

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COMMENT

The evidence is inconsistent about the association between testosterone therapy (TT) and subsequent risk of cardiovascular events (1). According to some guidelines, such as those of the American Urological Association (AUA), we should measure hemoglobin and hematocrit and inform patients about the increased risk of polycythemia before offering TT (2). According to the European Urological Association (EAU) guidelines, a hematocrit (HCT) > 54% should require testosterone therapy withdrawal, reduction of dose, change of formulation or venesection to avoid any cardiovascular events (3). However, it is not known if TT increases the risk of cardiovascular and thromboembolic events and what the safe hematocrit cutoff value is.

In this study, the authors tried to find the unsafe hematocrit threshold for men receiving TT and determine whether secondary polycythemia among men receiving TT causes an increased risk of major adverse cardiovascular events (MACE) and venous thromboembolic events (VTE). They performed a retrospective cohort study from a database of 74 million people including two groups of men with low testosterone who received TT and subsequently either did or did not develop polycythemia, and compared 5,842 men in each group. Polycythemia was defined as a hematocrit above 52%, in keeping with the AUA guideline definition. The primary outcome was incidence of MACE and VTE in the first year of TT. The authors found that men

on TT who developed secondary polycythemia had a higher incidence risk of MACE and VET than men who did not develop polycythemia. Moreover, they reported that hypogonadal men on TT versus those off testosterone had similar rates of MACE/VTE in the absence of polycythemia (4).

This study has some limitations. The TT group consisted of men who received two prescriptions for TT within nine months and the authors did not specify what modalities of testosterone were used (ex. gel, shorter- or longer-acting injection). Baseline hematocrit was greater in the polycythemia group (47.4%) versus the non-polycythemia group (42.5%). Nevertheless, I congratulate everyone involved in this study, which is the first to establish secondary polycythemia from TT as an independent risk factor for MACE/VTE using a specific hematocrit-based cutoff. This cutoff can guide our clinical practice and we can tell patients undergoing TT that they are at a higher risk of MACE and VTE if their hematocrit reaches or exceeds 52% during the first year of therapy. Despite these findings, further studies are needed to confirm the association between TT dosage and patient adherence to secondary polycythemia and MACE/VTE.

CONFLICT OF INTEREST

None declared.

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Editorial Comment: The effect of low-intensity shock wave therapy on moderate erectile dysfunction: A double-blind, randomized, sham-controlled clinical trial

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COMMENT

The undeniably numerous advances in the treatment of erectile dysfunction (ED) over the last two decades have not been able to satisfy the desire to search for a treatment modality capable of altering the underlying pathophysiology of the erectile mechanism. The search for a new modality of clinical treatment that is effective with a lasting effect that restores spontaneous erection has brought the focus of recent studies to a promising modality through low-intensity shock wave therapy (LiST), being treated as one of the treatments that has been increasingly proposed.

In 2010, when Vardi et al. first reported the use of LiST for ED (1), the proposed treatment has proven to produce structural changes that regenerate penile tissue, resulting from focused shock waves that interact with the target tissue, induced mechanical stress, and local microtrauma, generating a response with local angiogenic mediators that ultimately promote neovascularization of affected tissues and increase blood flow. The use in vasculogenic ED is postulated as the only currently marketed treatment that can offer a cure, which is the most desired outcome for most men suffering from ED, as outlined in the European Society of Urology guidelines. (2-5).

Despite the promising scenario, prospective randomized studies are scarce, conflicting with many unresolved questions. Furthermore, several aspects make it difficult to perform qualitative studies, such as the heterogeneity among shock wave generators, the type of shock waves emitted, and treatment proto-

cols (duration of treatment, number of sessions per week, total number of delivered shock wave pulses, and penile application sites).

This very interesting article by Kalyvianakis et al., (6) offers another step in our long journey ahead. Through a double-blind, randomized clinical trial controlled by Sham, the effect of Low Intensity Shockwave Therapy on moderate erectile dysfunction was evaluated.

Seventy men aged 40 to 70 years, in heterosexual relationships, stable for more than 3 months, with clinically diagnosed erectile dysfunction, were randomized to 12 sessions of LiST or sham therapy (35 patients) twice a week. Patients were evaluated 1 and 3 months after the end of treatment. The results of the present study suggest that LiST is effective and safe for moderate vasculogenic erectile dysfunction as more than two-thirds of patients showed significant improvement on the IIEF--EF scale.

However, some relevant aspects need to be highlighted. The assessment of vasculogenic ED, one of the inclusion criteria, was defined by clinical criteria that were not clearly described in the present study. The lack of objective data on the presence of vasculogenic erectile dysfunction such as the penile doppler or penile elastography, or even the description of underlying comorbidities, overshadows the underlying clinical condition. Stratifying the results according to comorbidities (hypertension, diabetes, obesity, dyslipidemia, etc), observing groups with more severe comorbidities, independently of the IIEF, could allow us to observe an association between severe pathologies (greater damage to the corpora cavernosa) and negative impact on the effect of LiST (7-9).

Moreover, regarding the application technique, no figure was described or presented application points (penile shaft, crura), making it difficult to understand the standardization of the method, in addition to no report if the treatment was performed by a single applicator or even if there was some prior training.

Corroborating with previous observations, phosphodiesterase type 5 (PDE5) inhibitor or other erectile dysfunction treatments were prohibited during the entire treatment / follow-up period. The strategy to eliminate the bias of an effect of PDE5 inhibitors is interesting, but the question remains: could this class of drugs optimize the local action of shock wave therapy? Future studies using this class of drugs versus placebo would be interesting to rule out this hypothesis.

Other limitations of the present study, appropriately mentioned by the authors, are the profile of patients from a single institution, the total n (70) and the profile of patients - exclusively with moderate ED. Furthermore, the short follow-up period (1 and 3 months) precludes conclusions regarding durability and peak of effect.

To conclude, we see in this important article one more confirmation of the effect of LiST, highlighting the importance of advancing in this field. It seems that LiST is here to stay, perhaps not as a major turning point in the treatment of ED but as a good adjuvant therapy applicable to a selected group of patients, capable of influencing and modifying outcomes.

CONFLICT OF INTEREST

None declared.

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Editorial Comment: Radical prostatectomy without prior biopsy following multiparametric magnetic resonance imaging and prostate-specific membrane antigen positron emission tomography

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COMMENT

Recently published in European Urology, Meissner et al (1) presented a series of 25 patients undergoing radical prostatectomy without performing a prostate biopsy, basing the surgical approach on the combination of multiparametric prostate resonance imaging (mpMRI) and prostate-specific membrane antigen positron emission tomography (PET-PSMA). Using the criterion of PIRADS≥4 and PET-Score≥4, 25 patients presented 100% of ISUP≥2. Despite the result found, we must be aware of the various weaknesses of the study and the potential repercussions that may be erroneously considered.

The aforementioned study is a retrospective analysis, with a small number of patients, and some ethical issues to consider. The approach certainly shows the potential of imaging risk stratification but simultaneously falls into the controversial field of cancer treatment without pathology support and patient exposure to the morbidity of radical prostatectomy. Although it was described that the patient was extensively instructed on the need for a prostate biopsy to better understand the disease and, then, to define the available therapeutic options (active surveillance, focal therapy, surgery, or radiotherapy), the surgical

procedure was performed without the biopsy. Our biggest concern is that some urologists, considering these data, may indicate surgery without biopsy in clinical practice without a research protocol and an approved informed consent.

In those patients in which radiotherapy was chosen, it was strictly necessary to perform a prostate biopsy to define the applied dose and evaluate the association with hormonal therapy. However, the same need also applies to the surgical approach, as it is paramount to define whether or not to perform extended lymphadenectomy, a procedure with considerable morbidity, and the criterion used for its performance is not described in the study.

To decide whether or not to perform lymphadenectomy, we still use clinic-pathological nomograms associated with MRI to help us in the decision. There is a tendency to perform less lymphadenectomy because its oncological role has been questioned (2, 3), but we still do not have data that support that PET-PSMA can replace these nomograms. In this way, patients may be undertreated by not performing lymphadenectomy when guided only by imaging exams.

In the supplementary material presented by the article, the author described that the sensitivity and positive predictive value (PPV) of mpMRI are 37% and 81%, respectively, and PET-PSMA has a sensitivity of 38% and a PPV of 81%. Using the combination of images, the sensitivity increased to 41% and PPV reached 80%. The author also described that sensitivity and PPV are slightly reduced in the lesion-based analysis using the criteria of PIRADS≥4 and PET-Score≥4. These numbers demonstrate the possibility of failure, both in the detection of the disease, with the loss of a patient with clinically significant prostate cancer (csPCa) and the possibility of failure in the diagnosis, with a chance of finding a lesion that would not require treatment or be a candidate for a less morbid approach, leading to over-treatment.

A recent meta-analysis published by Satapathy (4) shows that PET-PSMA sensitivity, specificity, positive likelihood ratio, and negative likelihood ratio for detection of csPCa were 0.99 (95% CI, 0.88– 1.00), 0.49 (95% CI, 0.36–0.62), 1.9 (95% CI, 1.5–2.5), and 0.02 (95% CI, 0.00–0.28), respectively. Considering a subgroup of initial detection of csPCa (ISUP>2), the study presents 1 case of a false negative in a population of 25 patients and the false positive rate varies between 4 and 50% in the included studies.

According to Emmet et al (5), the combination of MRI+PSMA showed that of 129 patients with a non-clinically significant tumor, the combination of imaging exams demonstrated a positive lesion in 78 patients (60%). The sensitivity of the combination of tests was 97%, specificity 40%, PPV 67%, and negative predictive value (NPV) 91%. The false negative rate was high, 17% on MRI and 10% on PSMA. Eiber et al (6) showed that the accuracy of the combination of MRI+PET-PSMA was 88%, sensitivity 76%, and specificity 97%. Thus, it is a consensus in the current literature that the MRI+PET-PSMA combination still does not have sufficient strength to determine csPC lesions.

Scheltema et al (7) performed a study using the mpMRI PIRADS 4–5 and PET-PSMA combination in 56 patients, the sensitivity, specificity, NPV, and PPV were 92%, 90%, 96%, and 81%, respectively. These percentages are based on patients already diagnosed with intermediate and high-risk prostate cancer. An approach with a combination of these imaging tests in patients without the diagnosis would most likely have lower rates.

The authors report that 100% of the patients had a csPCa, however, as it is a retrospective study with a low number of patients, it is difficult to understand important flaws in the selection criteria of the included patients. It would only be possible to draw some conclusions by studying the entire sample of the service with the same profile as the patients studied in this paper.

There are a few urological tumors treated without previous biopsy. Among them, we can mention adrenal, kidney, and testicular neoplasm. In these cases, image analysis has high accuracy and a low false positive rate for tumor detection. The delay in diagnosis can negatively impact patient survival and the result would not change the technical approach. In addition, performing the biopsy may alter the tumor staging or there is a risk of dissemination through the biopsy puncture site. All these criteria do not apply to prostate cancer and surgery may exposes patients to a negative impact on quality of life.

The prostate biopsy provides more information about the aggressiveness of the tumor, making possible a more conservative approach, whether by active surveillance or more recently partial gland ablation with well-known side effects such as sepsis (<1.5%), urinary retention (<2%), or hematuria requiring catheterization (<1%). Currently, lower complication rates are seen with the transperineal approach (8).

Currently, the challenge is to understand tumor biology, using analyzes such as Decipher, Oncotype, and other tests, to understand which patients, have cancer-specific survival benefits and may have an advantage from local treatment and to give a personalized approach. The proposal of aggressive local treatment of prostate cancer is opposed to the current search for lower morbidity treatment options.

We have been rapidly evolving in the diagnostic methods deployed in the prostate cancer pathway. It is our humble belief that imaging is not yet accurate enough to indicate radical treatment based on the combination of mpMRI+PET-PSMA information.

We commend Meissner et al (1) for their broad vision and motivation to explore novel approaches, but in this scenario, we would first need a study with a rigid methodology comparing radiological findings with both biopsy and final pathology. This could indeed create a more reliable clinical path to eventually offer radical prostatectomy without biopsy.

CONFLICT OF INTEREST

None declared.

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VIDEO SECTION

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Robotic approach to vesicourethral anastomotic stenosis and resection of remaining prostate after radical prostatectomy

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ABSTRACT

Objective: To show a total transabdominal robotic approach to an extensive recalcitrant vesicourethral anastomotic stenosis (VUAS) after open radical prostatectomy (ORP) with end-to-end anastomosis. While there is very little literature on the matter and even fewer videos showing the actual surgical view with a step-by-step explanation in complex cases, VUAS robotic transabdominal surgery provides better view and reach, with potentially better continence results, without the need for pubectomy.

Methods: A 72-year-old male was submitted to a failed ORP for Gleason 3+4 localized cancer 2 years before, where the wrong plane of dissection left behind prostate remnants and the seminal vesicles, which evolved with a complex stenosis and recurrent episodes of acute urinary retention (AUR) that started two weeks after the first catheter removal. Five endoscopic procedures in total were unsuccessful and AUR reoccurred. A vesico-urethral cystography (VUC) and multiparametric prostate and urethral MRI found the seminal vesicles with prostate remnants, two centimeters urethral stenosis from bladder neck to bulbar urethra and periurethral fibrosis with no evidence of residual tumor. PSA was 1.2 and prostate biopsy showed no tumor on prostate remnant. A transabdominal robotic approach was chosen.

Results: Prostate residue, bladder neck and periurethral fibrosis were excised, with healthy mucosa found on both ends. End-to-end anastomosis was successful. Drain and catheter were removed on the 1st and 14th post-operative day, respectively, with good urinary stream. A VUC at 30 days showed a patent bladder neck. Incontinence was 3 pads/day after catheter removal and decreased to 1 pad/day after 180 days.

Conclusion: VUAS may reach 15% (1, 2) and endourologic therapies are first-line choices, however, recalcitrant cases require reconstruction (3-6). The most common approach is perineal, with high incontinence rates, reaching >90% (7, 8). The retropubic alternative has better but also discouraging numbers of up to 58% incontinence rates (9). Though with 100% social continence results, the 2021 European guidelines still could not recommend the robotic procedure as standard of care due to evidence limited to anecdotal reports (10-12).

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

CONFLICT OF INTEREST

None declared.

COMPLIANCE WITH ETHICAL STANDARDS

Research involving Human Participants: The authors certify that the study was performed under the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

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VIDEO SECTION

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ASTRA – An alternative approach for the posterior urethra

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ABSTRACT

Introduction: Access represents one of the main challenges in performing posterior urethroplasty (1, 2). Several approaches and tactics have been previously described (3). This video demonstrates the Anterior Sagittal Transrectal Approach (ASTRA), which allows better visualization of the deep perineum (4).
Materials and Methods: Our patient was a 65-year-old man with post radical prostatectomy vesicourethral anastomotic stenosis. He failed repeated endoscopic interventions, eventually developing urinary retention and requiring a cystostomy. We offered a vesicourethral anastomotic repair through ASTRA. The patient was placed in the jackknife position and methylene blue instilled through the cystostomy. To optimize access to the bladder neck, an incision of the anterior border of the rectum is performed. Anastomosis is carried out with six 4-0 PDS sutures. These are tied using a parachute technique, after insertion of a 16F Foley.
Results: The patient was discharged after 72 hours, and the Foley catheter was removed after 4 weeks. There were no access-related complications. Retrograde urethrogram 3 months after surgery confirmed patency of the anastomosis. Upon review 5 months after surgery the patient had urinary incontinence requiring 5 pads/day and was considered for an artificial urinary sphincter.
Discussion: In our series of 92 patients who have undergone reconstructive procedure through ASTRA there have been no cases of fecal incontinence. Two patients with prior history of radiotherapy developed rectourethral fistulas. Urinary incontinence was observed in those patients with stenosis after radical prostatectomy.
Conclusion: This video presents a step-by-step description of ASTRA, an approach that provides excellent visualization to the posterior urethra, representing an alternative access for repair of complex posterior urethral stenosis.

CONFLICT OF INTEREST

None declared.

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LETTER TO THE EDITOR

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Re: Long term outcomes of one-stage augmentation anterior urethroplasty: a systematic review and meta-analysis

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To the editor,

We recently read an article, entitled "Long term outcomes of one-stage augmentation anterior urethroplasty: a systematic review and meta-analysis" (1). The authors summarized and concluded the long-term success of anterior augmentation urethroplasty (AU) from 10 published researchers.

Previous studies showed the success rates for augmentation urethroplasty was around 85%, yet this is an exaggerated rate as the rate declines over time according to this article. The authors claimed that the long-term success of augmentation urethroplasty seemed not as durable as reported with intermediate follow-up and showed to have continued deterioration with more than 100 months of follow-up. We are interested in the authors' work as many doctors and patients ignore this in clinical practice. The decreasing effectiveness of AU during long-term follow-up reminds clinicians of the need to reassess this procedure and the need to inform patients about this progress.

With all due respect, there are some controversies need to be clarified. First, 10 retrospective studies were analyzed in this article. We found that patients could be recruited repeatedly in 2 researchers performed by Barbagli et al. in 2008 (2) and 2009 (3). The article published in 2009 was a brief report regarding outcomes of repair of penile urethral strictures using one-stage flap or graft urethroplasty with a maximum follow-up of 132 months. As a result, there could be duplicated data in these 2 articles.

Second, assessing the quality of included studies in meta-analyses is necessary. Generally, the Newcastle-Ottawa Scale is one of the most popular tools applied in non-randomized studies. Even if all included studies were observational studies, the authors did not give a detailed evaluation, which could undermine the rigorousness of this research.

Third, a funnel plot is not necessary to detect publication bias when there were less than 10 researchers, as symmetries are difficult to tell on this occasion. It would be perfect if some other tools, such as Egger test, had been applied in the analysis of publication bias.

Finally, the authors insightful work will inspire more similar studies and we are thankful for their contributions.

The Author

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Ke Lu and Yongchang Chen contributed equally to the work as co-first authors

CONFLICT OF INTEREST

None declared.

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REPLY TO THE AUTHORS: Re: Long term outcomes of one-stage augmentation anterior urethroplasty: a systematic review and meta-analysis

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To the editor,

We appreciate the editorial comments on our manuscript (1, 2). Unfortunately, the reconstructive urology urethroplasty literature is almost all retrospective and cohort sizes are relatively small. Moreover, only a few papers report interim or long-term follow up success. It is because of the very limitations and weaknesses of the urethroplasty literature that we needed to perform a systematic review and meta-analysis. We closely followed the PRISMA method here and understand the critique of not utilizing the Newcastle-Ottawa Scale to assess the studies. The main take home of our analysis is that the "85% success rate" that is often quoted preoperatively to patients appears to be a clear over -estimation of the success of augmentation urethroplasty. Despite the inherent limitations of the literature, our manuscript clearly shows that augmentation urethroplasty has a slow and progressive recurrence rate overtime. The longer the follow up the more recurrences are identified. Augmentation urethroplasty demonstrates good success at intermediate follow-up, but with longer follow up it appears that it is not the panacea that it is commonly thought.

The authors.

CONFLICT OF INTEREST

None declared.

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In response to the concerns of the editors of scientific medical journals with ethics, quality and seriousness of published articles, a Committee on Publication Ethics (COPE) was established in 1997 and a guideline document was published. The International Braz J Urol signed, approved, and follows the COPE guidelines. The Editor strongly encourages the authors to carefully read these guidelines before submitting a manuscript **(www.publicationethics.org.uk/guidelines or www.brazjurol.com.br**, vol. 26 (1): 4-10, 2000).

Peer Review – All submissions are subject to editorial review. Typically, each manuscript is anonymously forwarded by the Editor to 4 Reviewers (at least 2). If the Editor receives conflicting or inconclusive revisions, the manuscript is always sent to 1 or 2 additional Reviewers before the Editor's decision. If considered necessary by the Editor or by the Reviewers, statistical procedures included in the manuscript will be analyzed by a statistician.

The **International Braz J Urol** contains six sections: **Original Article, Review Article, Surgical Technique, Challenging Clinical Case, Radiology Page**

and **Video Section**. The articles should be written in Portuguese or English official orthography.

Abbreviations should be avoided, and when necessary must be specified when first time mentioned. Unusual expressions may not be used. A list of abbreviations must be provided at the end of the manuscript.

Every manuscript submitted to publication should have a cover page containing the title, short title (up to 50 characters), authors and institution. Up to six key words should be provided. These words should be identical to the medical subject headings (MeSH) that appear in the Index Medicus of the National Library of Medicine **(http://www.nlm.nih.gov/mesh/meshhome.html)**. One of the authors should be designated as correspondent and the complete correspondence address, telephone and fax numbers and E-mail should be provided.

If any financial support has been provided, the name of the institution should be mentioned.

Original Article: Original articles should contain a Cover Page, Abstract, Introduction, Materials and Methods, Results, Discussion, Conclusions, References, Tables and Legends, each section beginning in a separate page and numbered consecutively. Original articles should cover contemporary aspects of Urology or experimental studies on Basic Sciences applied to urology. The manuscript text should contain no more than 2500 words, excluding the Abstract. The number of authors is limited to five. References should contain no more than 30 citations, including the most important articles on the subject. Articles not related to the subject must be excluded.

Review Article: Review articles are accepted for publication upon Editorial Board's request in most of the cases. A Review Article is a critical and systematic analysis of the most recent published manuscripts dealing with a urological topic. A State of the Art article is the view and experience of a recognized expert in the topic. An abstract must be provided.

Surgical Technique: These manuscripts should present new surgical techniques or instruments and should contain Introduction, Surgical Technique, Comments and up to five References. An abstract must be provided. At least five cases performed with the technique must be included.

Challenging Clinical Case: These manuscripts should present relevant clinical or surgical situations which can bring or consolidate our understanding of genesis, natural history, pathophysiology and treatment of diseases. *Structure of the articles*

Abstract (maximum 200 words) and should contain

- **Main findings:** Report case(s) relevant aspects
- **Case(s) hypothesis:** Proposed premise substantiating case(s) description
- **Promising future implications:** Briefly delineates what might it add? Lines of research that could be addressed

Full text (maximum 2000 words):

- **Scenario:** Description of case(s) relevant preceding and existing aspects;
- **Case(s) hypothesis and rational:** precepts, clinical and basic reasoning supporting the case(s) hypothesis and the raised scenario. Why is it important and is being reported?
- **Discussion and future perspectives:** what might it add and how does it relate to the current literature. 'Take-home message' - lessons learnt;
- **Table and/or Figure limits:** 2 (plates aggregating multiple images are encouraged) each exceeding table or figure will decrease 250 words of the full text;
- **Number of references:** 10-15.

Radiology Page: Will be published upon the Section Editor decision.

Video Section: The material must be submitted in the appropriate local, in the Journal's site, whe-

re all instructions may be found (Video Section link) Letters to the Editor: The letter should be related to articles previously published in the Journal, should be useful for urological practice and must not exceed 500 words. They will be published according to the Editorial Board evaluation.

ILLUSTRATIONS:

The illustrations should not be sent merged in the text. They should be sent separately, in the final of the manuscript.

1) The number of illustrations should not exceed 10 per manuscript.
2) Check that each figure is cited in the text.
3) The legends must be sent in a separate page.
4) The legends of histological illustrations should contain the histological technique and the final magnification.
5) The International Braz J Urol encourages color reproduction of illustrations wherever appropriate.
6) All histological illustrations should be supplied in color.

ELECTRONIC SUBMISSION:

1) Do not embed the figures in the text, but supply them as separate files.
2) For Submitting Photographs Electronically, please:
Supply photographs as TIFF (preferable) or JPG files. The TIFF of JPG should be saved at a resolution of 300 dpi (dots per inch) at final size. If scanned, the photographs should be scanned at 300 dpi, with 125mm width, saved as TIFF file and in grayscale, **not embed in Word or PowerPoint.**
3) For Submitting Line Artwork Electronically please note that:
Line drawings must be supplied as EPS files (give an EPS extension, e.g. Fig01.eps). Use black text over light to mid grey and white text over dark grey or black shades. Use lower case for all labeling, except for initial capitals for proper nouns and necessary mathematical notation. Centre each file on the page and save it at final size with the correct orientation. We recommend a minimum final width of 65 mm, but note that artwork may need to be resized and relabeled to fit the format of the Journal.
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a) **DO NOT** embed the images in the text; save them as a separate file
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c) **DO NOT** supply photographs in PowerPoint or Word. In general, the files supplied in these formats are at low resolution (less than 300 dpi) and unsuitable for publication.
d) **DO NOT** use line weights of less than 0.25 point to create line drawings, because they will nor appear when printed.

TABLES: The tables should be numbered with Arabic numerals. Each table should be typed on a single page, and a legend should be provided for each table. Number tables consecutively and cites each table in text in consecutive order.
REFERENCES: The References should be numbered following the sequence that they are mentioned in the text. The references should not be alphabetized. They must be identified in the text with Arabic numerals in parenthesis. Do not include unpublished material and personal communications in the reference list. If necessary, mention these in the body of the text. For abbreviations of journal names refer to the "List of Journals Indexed in Index Medicus" (http://www.nlm.nih.gov). The authors must present the references according to the following examples; the names of **all authors** must be included; when exist more than six authors, list the first six authors followed **by et al.** The **initial** and the **final** pages of the reference should be provided:

Papers published in periodicals:

▪ Paterson RF, Lifshitz DA, Kuo RL, Siqueira Jr TM, Lingeman JE: Shock wave lithotripsy monotherapy for renal calculi. Int Braz J Urol. 2002; 28:291-301.

▪ Holm NR, Horn T, Smedts F, Nordling J, de la Rossete J: Does ultrastructural morphology of human detrusor smooth muscle cell characterize acute urinary retention? J Urol. 2002; 167:1705-9.

Books:

▪ Sabiston DC: Textbook of Surgery. Philadelphia, WB Saunders. 1986; vol. 1, p. 25.

Chapters in Books:

▪ Penn I: Neoplasias in the Allograft Recipient. In: Milford EL (ed.), Renal Transplantation. New York, Churchill Livingstone. 1989; pp. 181-95.

The Int Braz J Urol has the right of reject inappropriate manuscripts (presentation, number of copies, subjects, etc.) as well as proposes modifications in the original text, according to the Referees' and Editorial Board opinion.

THE EDITORS SUGGEST THE AUTHORS TO OBSERVE THE FOLLOWING GUIDELINES WHEN SUBMITTING A MANUSCRIPT:

The **Ideal Manuscript** may not exceed 2500 words.

The **Title** must be motivating, trying to focus on the objectives and content of the manuscript.

Introduction must exclude unnecessary information. It should briefly describe the reasons and objective of the paper.

Materials and Methods should describe how the work has been done. It must contain sufficient information to make the study reproducible. The statistical methods have to be specified.

The **Results** should be presented using Tables and Figures whenever possible. Excessive Tables and Figures must be avoided. The tables should not be repeated on the text.

The **Discussion** must comment only the results of the study, considering the recent literature.

Conclusions must be strictly based on the study findings.

References should contain no more than 30 citations, including the most important articles on the subject. Articles not related to the subject must be excluded.

The Abstract must contain up to 250 words and must conform to the following style: Purpose, Materials and Methods, Results and Conclusions. Each section of the manuscript must be synthesized in short sentences, focusing on the most important aspects of the manuscript. **The authors must remember that the public firstly read only the Abstract, reading the article only when they find it interesting.**

NOTE:

Recent issues of the International Braz J Urol must be observed concerning the presentation form of the manuscript.

MANUSCRIPT CHECKLIST

The authors should observe the following checklist before submitting a manuscript to the **International Braz J Urol**

- The sequence of manuscript arrangement is according to the Information for Authors.
- The Article is restricted to about 2,500 words and 6 authors.
- Abbreviations were avoided and are defined when first used and are consistent throughout the text.
- Generic names are used for all drugs. Trade names are avoided.
- Normal laboratory values are provided in parenthesis when first used.
- The references were presented according to the examples provided in the Information for Authors. The references were numbered consecutively, following the sequence that they are mentioned in the text. They were identified in the text using Arabic numeral in parenthesis. The names of all authors were provided. When exist more than six authors, list the first sixauthors followed by et al. The initial and the final pages of the reference should be provided. The number of references must be accordingly to the informed in the Instructions for Authors, depending on the type of manuscript.
- The staining technique and the final magnification were provided for all histological illustrations. The histological illustrations are supplied in color.
- Legends were provided for all illustrations, tables, and charts. All tables and charts were in separate pages and referred to in the text. All illustrations and tables are cited in the text.
- An Abstract was provided for all type of articles. The length of the Abstract is about 250 words.
- A corresponding author with complete address, telephone, Fax, and E-mail are provided.
- A submission letter and a disclosure form, signed by all authors, are included.
- The authors should included written permission from publishers to reproduce or adapt a previously published illustrations or tables.
- **Conflict of Interest** – Any conflict of interest, mainly financial agreement with companies whose products are alluded to in the paper, is clearly disclosed in the manuscript.
- **Check that each figure is cited in the text. The illustrations are not merged in the text.**
- The photographs are supplied as TIFF or JPG files and saved at a resolution of 300 dpi (dots per inch) at final size.
- The photographs should be scanned at 300 dpi, with 125mm width, saved as TIFF file and in grayscale, not **embed in Word or PowerPoint.**
- A list of abbreviations is provided.