

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	The current status and progression of lower urinary tract symptoms in Chinese male patients: the protocol and rationale for a nationwide, hospital-based, prospective, multicenter study
AUTHORS	Song, Qi-Xiang; Zhang, Yi; Ye, Xiaofei; Xue, Wei; Xu, Chuanliang; Xu, Jing; Abrams, Paul; Sun, Yinghao

VERSION 1 – REVIEW

REVIEWER	Naomi Noguchi The University of Sydney, Australia
REVIEW RETURNED	19-Feb-2019

GENERAL COMMENTS	<p>P4 L47, P10 L40 "cross-sectional; assessment" This should be called a baseline assessment although I understand that this will serve as cross sectional data to make comparisons across different cohorts.</p> <p>P4 L54 "allocated to receive prostate surgery" This sounds like it is a trial rather than an observational study. Please clarify in the abstract that the 24-month follow-up starts when patients receive the surgeries.</p> <p>P8 L22 Direction of causality References 10 to 12 only found that lower urinary tract symptoms and elevated serum creatinine levels often coexist, but does not indicate direction of causality (LUTS damaged kidney). It is also possible that LUTS is merely a marker of elevated creatinine due to underlying causes to both conditions.</p> <p>P12 L47 Exclusion criteria Patients with obvious mechanical and pathological causes of LUTS were excluded. However, the resultant cohort will still include idiopathic LUTS that are not caused by enlarged prostate such as detrusor overactivity and underactivity. Is the aim of the inclusion/exclusion criteria to limit to idiopathic LUTS rather than to limit to prostate enlargement?</p> <p>P13 L40 Treatment protocol Please clarify if this guideline was part of treatment protocol, recommended, distributed across the participating hospitals or endorsed by academic bodies such as the local surgeon's college. If not the guideline should not be mentioned and say "patients will be treated according to the standard practice of each institution".</p> <p>p14 L47 Translated versions of the questionnaire</p>
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	<p>It is great that validate questionnaires were used. If a translated version was used, please provide references of validation studies of the translated questionnaires.</p> <p>P17 L1 Measurement of PVR Please clarify how PVR will be measured (catheter? Ultrasound? Portable scanner?).</p> <p>P23 L22 Effect of treatment An observational study cannot answer questions about treatment effect because they are inherently prone to confounding. However, this study will be a good prognostic study in a (reasonably) representative population reflecting the local medical practice.</p>
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REVIEWER	<p>Julien Renard Division of Urology , Ente Ospedaliera Cantonale, Ospedale San Giovanni Bellinzona, Switzerland</p> <p>Consultant Geneva University Hospital, Geneva, Switzerland</p>
REVIEW RETURNED	19-Feb-2019

GENERAL COMMENTS	<p>This paper aims at evaluating LUTS among middle aged chinese male patients and investigate the changes of both conditions after intervention through a two year prospective follow up. This paper has the role of presenting the study protocol.</p> <p>The main quality of the study lies in its design and the size of the population who will be studied making it a clear advantage. One of its limitations is the fact that it only treats of a single country and race Group (Asian) even though it is clear that the chinese population due to the size of the country and the extension of its borders surely bears great variability (compensating the above point)</p> <p>The study goal is to elucidate the symptom characteristics of LUTS and comorbidities of middle aged and elderly man in China" . However the study aims at excluding patients without obstructive enlarged prostate. (page 12 line 47). Although exclusion criteria in table 2 clearly exclude neurogenic bladder , oncologic patients etc etc, it is unclear if patients that may present idiopathic overactive- underactive bladder or patients presenting metabolic conditions that may alter bladder contractility (diabetes, chronic alcoholism etc etc) -groups that may and may not present "obstructed enlarged prostates" - will be included or excluded form the study.</p> <p>If so which criteria will be used to exclude- include them (BCI , BOOI) .</p> <p>It is important to clear that point to undertand if authors which to include exclusively patients with bladder outlet obstruction from prostate enlargement as it seems in paragraph 2.4</p> <p>- Another points that needs explanation is why do surgical patients will be followed starting at 1 month after prostate surgery while in the oral medication Group , follow up will start at the 6 month visit</p> <p>- I would clearly precise (stratify) in the oral medication Group patients who undergo treatment with chinese herbs and state which type of herbs are used</p>
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REVIEWER	Arturo Artero Universitat de València Hospital Univeritario Dr. Peset Valencia, Spain
REVIEW RETURNED	22-Feb-2019

GENERAL COMMENTS	<p>This is a protocol of a large-scale nationwide cohort study designed to investigate the characteristics of men with lower urinary tract symptoms as well as changes in urological symptoms and systemic comorbid conditions following either medication or surgical intervention. The study is well designed. The study flow diagram is easily understandable and its the objectives are clear, as well as the inclusion and exclusion criteria. The following comments should be addressed:</p> <ul style="list-style-type: none"> - The dates of the study should be included in the manuscript. - The patient's medical comorbidities should be clearly specified on the form. I suggest including in the protocol a list of medical conditions with the diagnosis criteria for each of them, especially for those medical conditions that could have influence on the symptoms analyzed in the study, e.g. COPD, sleep apnea... - I suggest performing a urine culture in cases where acute urinary tract infection is a probable cause of the patient's symptoms. A urinalysis could be not enough in these cases.
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VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: Naomi Noguchi

Institution and Country: The University of Sydney, Australia

Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below

P4 L47, P10 L40 "cross-sectional; assessment"

This should be called a baseline assessment although I understand that this will serve as cross sectional data to make comparisons across different cohorts.

We thank the reviewer for this suggestion. We have revised the wording in the text.

P4 L54 "allocated to receive prostate surgery"

This sounds like it is a trial rather than an observational study. Please clarify in the abstract that the 24-month follow-up starts when patients receive the surgeries.

We thank the reviewer for pointing this out. In this study, the selection of medications or surgical approach is based on the current guidelines as well as the clinician's own experience. We have revised this sentence to avoid misunderstanding.

P8 L22 Direction of causality

References 10 to 12 only found that lower urinary tract symptoms and elevated serum creatinine levels often coexist, but does not indicate direction of causality (LUTS damaged kidney). It is also possible that LUTS is merely a marker of elevated creatinine due to underlying causes to both conditions.

We thank the reviewer for this comment. Current literatures only indicate that chronic kidney disease is a risk factor of LUTS. However, the exact direction of causality is unknown. It may be true that

LUTS is a manifestation of renal dysfunction. On the contrary, long lasting bladder outlet obstruction can cause upper urinary tract dilation and hydronephrosis. It could be difficult to elucidate the direction of causality based on the current protocol or any existing literature.

P12 L47 Exclusion criteria

Patients with obvious mechanical and pathological causes of LUTS were excluded. However, the resultant cohort will still include idiopathic LUTS that are not caused by enlarged prostate such as detrusor overactivity and underactivity. Is the aim of the inclusion/exclusion criteria to limit to idiopathic LUTS rather than to limit to prostate enlargement?

Thanks to the reviewer for raising this concern. We tend to include LUTS patients with an enlarged prostate which is likely to cause obstruction. We excluded LUTS caused by stricture, stone and tumor etc because prostate surgery or LUTS related medications are not standard treatments. Detrusor overactivity and underactivity may occur as a result of an enlarged prostate and can also be idiopathic.

P13 L40 Treatment protocol

Please clarify if this guideline was part of treatment protocol, recommended, distributed across the participating hospitals or endorsed by academic bodies such as the local surgeon's college. If not the guideline should not be mentioned and say "patients will be treated according to the standard practice of each institution".

We thank the reviewer for the suggestion. We have stated in the text that "The selection of surgical approach is based on the current guidelines as well as the surgeon's own experience".

P14 L47 Translated versions of the questionnaire

It is great that validate questionnaires were used. If a translated version was used, please provide references of validation studies of the translated questionnaires.

Thanks to the reviewer for raising this concern. The three questionnaires have all been previously validated via several studies. However, only the validation of the IPSS scores was published in English language, while other two were validated in some Chinese studies. We have added reference citation in the text.

P17 L1 Measurement of PVR

Please clarify how PVR will be measured (catheter? Ultrasound? Portable scanner?).

We thank the reviewer for pointing this out. The PVR will be measured via ultrasound. The related information can be found in section 2.7.6.

P23 L22 Effect of treatment

An observational study cannot answer questions about treatment effect because they are inherently prone to confounding. However, this study will be a good prognostic study in a (reasonably) representative population reflecting the local medical practice.

We thank the reviewer for this suggestion. We totally agree. Actually, instead of assessing the treatment outcome during the follow-up, we tend to focus on the changes of comorbidities which will be assessed by laboratory tests and their potential association with the change of LUTS. We have revised the sentence and inserted the reviewer's suggestions in the text.

Reviewer: 2

Reviewer Name: Julien Renard

Institution and Country:

Division of Urology , Ente Ospedaliera Cantonale, Ospedale San Giovanni Bellinzona, Switzerland
Consultant Geneva University Hospital, Geneva, Switzerland

Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below

- This paper aims at evaluating LUTS among middle aged chinese male patients and investigate the changes of both conditions after intervention through a two year prospective follow up. This paper has the role of presenting the study protocol.

The main quality of the study lies in its design and the size of the population who will be studied making it a clear advantage. One of its limitations is the fact that it only treats of a single country and race Group (Asian) even though it is clear that the chinese population due to the size of the country and the extension of its borders surely bears great variability (compensating the above point) We thank the reviewer for the positive comment.

- The study goal is to elucidate the symptom characteristics of LUTS and comorbidities of middle aged and elderly man in China" . However the study aims at excluding patients without obstructive enlarged prostate. (page 12 line 47). Although exclusion criteria in table 2 clearly exclude neurogenic bladder, oncologic patients etc etc, it is unclear if patients that may present idiopathic overactive-underactive bladder or patients presenting metabolic conditions that may alter bladder contractility (diabetes, chronic alcoholism etc etc) -groups that may and may not present" obstructed enlarged prostates" - will be included or excluded from the study. If so which criteria will be used to exclude-include them (BCI, BOOI). It is important to clear that point to understand if authors which to include exclusively patients with bladder outlet obstruction from prostate enlargement as it seems in paragraph 2.4

We thank the reviewer for the raising this concern. We tend to include LUTS patients with an enlarged prostate which is likely to cause obstruction. As mentioned in the protocol, not all subjects will undergo urodynamic tests, so we're not just recruiting patients with benign prostatic obstruction. A man presenting overactive or underactive bladder along with an enlarged prostate is a candidate for this study.

- Another points that needs explanation is why do surgical patients will be followed starting at 1 month after prostate surgery while in the oral medication Group, follow up will start at the 6 month visit We thank the reviewer for the raising this concern. Surgery may not cure all LUTS and can lead to de novo storage symptoms. Therefore, the 1-month timepoint was designed to study the patients' short-term symptoms and complications following surgery, in comparison with the data before surgery and at 6 months follow-up timepoint.

- I would clearly precise (stratify) in the oral medication Group patients who undergo treatment with chinese herbs and state which type of herbs are used We thank the reviewer for this constructive suggestion. We do have some doctors use traditional Chinese herbs to treat patients with LUTS nowadays, but most of them are not urologists. Since the participants are patients present in urology department, those who managed by Chinses herbs are likely to be excluded. But we will carefully document the type of herbs during study and hopefully can perform subgroup analysis to look into the effects of Chinese herbs and first-line medications.

Reviewer: 3

Reviewer Name: Arturo Artero

Institution and Country: Universitat de València

Hospital Univeritario Dr. Peset

Valencia, Spain

Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below

- This is a protocol of a large-scale nationwide cohort study designed to investigate the characteristics of men with lower urinary tract symptoms as well as changes in urological symptoms and systemic comorbid conditions following either medication or surgical intervention. The study is well designed. The study flow diagram is easily understandable and its the objectives are clear, as well as the inclusion and exclusion criteria. The following comments should be addressed:

- The dates of the study should be included in the manuscript.

We thank the reviewer for this suggestion. We have revised the Trial status section as follow: "The first patient was recruited on Apr 20th, 2018 and clinical data from 500 subjects have been collected by Nov 1st, 2018".

- The patient's medical comorbidities should be clearly specified on the form. I suggest including in the protocol a list of medical conditions with the diagnosis criteria for each of them, especially for those medical conditions that could have influence on the symptoms analyzed in the study, e.g. COPD, sleep apnea...

We thank the reviewer for this suggestion. We didn't provide detailed diagnosis criteria because the comorbidities are based on patients' self-report or their past medical records. We have listed the major medical conditions in the text as you suggested.

- I suggest performing a urine culture in cases where acute urinary tract infection is a probable cause of the patient's symptoms. A urinalysis could be not enough in these cases.

We thank the reviewer for this suggestion. We totally agree that urine culture is more precise than urinalysis and we have considered using urine culture to detect acute urinary tract infection in the first place. However, we chose urinalysis because of two main reasons. Firstly, because the urine culture usually takes days, patients who had surgery may have been discharged from hospital before we know the results, and those who present at the clinic are less willingly to participate the study. Secondly, urinalysis is the recommended primary evaluation for urinary tract infection by the EAU guidelines.

VERSION 2 – REVIEW

REVIEWER	Naomi Noguchi University of Sydney, Australia
REVIEW RETURNED	28-Jun-2019

GENERAL COMMENTS	<p>This is a protocol of a multi centre prospective cohort study to determine the clinical course of male LUTS that are treated by urologists. It will be a useful study to describe clinical course of male LUTS based on the contemporary local diagnostic and therapeutic practice in China and may also clarify how LUTS interact with systemic diseases.</p> <p>I am satisfied with all the authors' responses to my previous enquiries and would only like to suggest one minor revision as follows.</p> <p>page 51 line 8-12 "The goalenlarged prostate"</p> <p>The set of inclusion/exclusion criteria seems to aim to exclude LUTS with apparent mechanical, infectious, iatrogenic, or neurological causes rather than to limit to LUTS caused by enlarged prostate. This statement also contradicts to the introduction and discussion sections where the authors acknowledge the diverse etiology of LUTS as opposed to historic focus on prostate enlargement.</p> <p>Otherwise, I am excited to see their future publications and would like to wish the research team all the best.</p>
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REVIEWER	Julien Renard Ente ospedaliera cantonale , ORBV division of Urology , Bellinzona, Switzerland Geneva university Hospital , division of urology , Geneva , Switzerland
REVIEW RETURNED	07-Jul-2019
GENERAL COMMENTS	Accept

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: Naomi Noguchi

Institution and Country: University of Sydney, Australia

Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below

This is a protocol of a multi-centre prospective cohort study to determine the clinical course of male LUTS that are treated by urologists. It will be a useful study to describe clinical course of male LUTS based on the contemporary local diagnostic and therapeutic practice in China and may also clarify how LUTS interact with systemic diseases.

I am satisfied with all the authors' responses to my previous enquiries and would only like to suggest one minor revision as follows.

page 51 line 8-12 "The goalenlarged prostate"

The set of inclusion/exclusion criteria seems to aim to exclude LUTS with apparent mechanical, infectious, iatrogenic, or neurological causes rather than to limit to LUTS caused by enlarged prostate. This statement also contradicts to the introduction and discussion sections where the authors acknowledge the diverse etiology of LUTS as opposed to historic focus on prostate enlargement.

Otherwise, I am excited to see their future publications and would like to wish the research team all the best.

Thank you. We have deleted the statement "The goal of inclusion/exclusion criteria...obstructing enlarged prostate" to avoid misunderstanding. Again, we appreciate all your valuable suggestions.

Reviewer: 2

Reviewer Name: Julien Renard

Institution and Country:

Ente ospedaliera cantonale , ORBV division of Urology , Bellinzona, Switzerland

Geneva university Hospital , division of urology , Geneva , Switzerland

Please state any competing interests or state 'None declared': None

Please leave your comments for the authors below

Accept

Thank you!