RESEARCH ARTICLE

REVISED Frequency and clinical significance of prostatic involvement in men with febrile urinary tract infection: a prospective observational study [version 2; peer review: 1 approved, 1 approved with reservations]

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Abstract

Background: Frequent asymptomatic involvement of the prostate has been demonstrated in men with febrile urinary tract infection (fUTI). In view of this, men with fUTI are often given a longer duration of antibiotic treatment; however, evidence to support this is limited.
Methods: We prospectively studied adult men with fUTI admitted under the Department of Medicine in a tertiary care hospital in southern India. fUTI was defined as fever of ≥38°C with at least one symptom/sign of UTI and pyuria, requiring hospitalization. We estimated serum total prostate-specific antigen (PSA) levels at enrollment, one month and three months after treatment completion. We assessed prostatic volume by transrectal ultrasonography (TRUS) and estimated the serum high sensitivity C-reactive protein (hs-CRP) levels at baseline and after three months.
Results: We enrolled 64 men (median [IQR] age 53 [45-60] years); 50 patients completed follow-up. At baseline, 24 (38%) of 64 patients had elevated serum PSA values compared to age-specific upper limit. The median (IQR) serum PSA level was 2.15 (1.18-3.02) ng/mL and median (IQR) serum hs-CRP level was 2.23 (1.85-2.74) mg/dL (N=64). At three months, serum PSA levels decreased by ≥25% in 47 (94%) of 50 patients. The median (IQR) of prostatic volume was 25.4 (18.9-34) mL at baseline (N=64), and ≥10% decrease in prostatic volume was observed in 24 (48%) of 50 patients at three months. The change in the serum PSA levels did not correlate with clinical findings like prostatic

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tenderness or with prostatic volume changes. Further, serum PSA levels did not correlate with hs-CRP levels. On follow-up, seven patients had lower urinary tract symptoms; only one of them had recurrent fUTI.
Conclusions: Asymptomatic prostatic involvement, although common in men with fUTI, does not seem to influence the treatment outcomes.

Keywords
urinary tract infections, prostate-specific antigen, men, prostatitis, antibiotic treatment duration

Any reports and responses or comments on the article can be found at the end of the article.

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REVISED **Amendments from Version 1**

In the revised version, we have specified the research question explicitly. We present the proportion of patients with elevated baseline serum PSA levels compared to the age-specific serum PSA levels in healthy adult men of same ethnicity. The important laboratory and imaging parameters at baseline and at 3 months is compared only in patients who have completed follow up. We also have modified tables and figures accordingly. We have corrected the error in the serum hs-CRP data.

Any further responses from the reviewers can be found at the end of the article

Introduction

Urinary tract infections (UTIs) in men are generally considered to be complicated UTIs because of increased prevalence of underlying structural and functional abnormalities[1]. One such abnormality is the possibility of involvement of the prostate gland during an episode of UTI. Symptomatic involvement of the prostate gland by acute bacterial infection, known as acute bacterial prostatitis (ABP), classically presents with fever and systemic symptoms along with pelvic pain and infravesical obstruction[2]. However, even in the absence of prominent voiding and storage symptoms, subclinical involvement of the gland is possible in men with febrile UTI (fUTI). A study of Swedish men with fUTI provided the major evidence for this, in the form of increased serum prostate-specific antigen (PSA) levels and prostatic volume during an episode of UTI[3]. Another study using ^{111}indium-labelled leukocyte scintigraphy found that, although often clinically unrecognized, the prostate was involved in most cases of fUTI and acute pyelonephritis in men[4].

Differentiating fUTI with subclinical prostatic involvement from classical ABP is important. First, some experts recommend that antibiotic treatment in men with fUTI should not only sterilize the urine but also achieve sufficient concentrations in the prostate. Fluoroquinolones and co-trimoxazole were recommended as optimal choices to achieve this aim[5,6]. If the increased levels of PSA are truly indicative of ABP, implementing this guidance would be pragmatically challenging in settings where antimicrobial resistance, especially to fluoroquinolones, is very common among uropathogens and other appropriate oral options are not available[7]. Second, while it is generally agreed that ABP requires antibiotic treatment for at least two to four weeks to prevent chronic prostatitis[8], it is unclear whether subclinical prostatic involvement would also necessitate a longer treatment. We, therefore, conducted the present study to answer the following research questions — i) What is the frequency of prostatic involvement in men with fUTI, and ii) Is prostatic involvement associated with recurrence of UTI?

Methods

Ethical statement

The study protocol was reviewed and approved by the Institute Ethics Committee (Human Studies) of Jawaharlal Institute of Postgraduate Medical Education and Research, Puducherry (JIP/IEC/2016/29/970). Written informed consent was obtained from all study participants.

Study setting

We conducted a prospective observational study in the medical wards of Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), a tertiary care hospital in Southern India, during July 2016 and May 2018. During this study period, we screened all consecutive male patients aged 18 years or over admitted under the Department of Medicine as suspected cases of fUTI for eligibility to participate in the study. We defined fUTI as documented fever of at least 38°C with at least one symptom or sign referable to the urinary tract such as dysuria, frequency, urgency, flank pain or renal angle tenderness. All patients had evidence of microscopic pyuria (>5 pus cells/hpf) or urine dipstick positive for leukocyte esterase. We excluded patients with catheter-associated UTI, urological procedures or surgery in the past four weeks, diagnosed with prostate carcinoma, or significant upper urinary tract obstruction evidenced by gross hydroureteronephrosis (HUN).

Study procedure

After obtaining written informed consent, the investigator (TSA) performed a standardized clinical evaluation. A digital rectal examination (DRE) was done to look for prostatic enlargement, tenderness or bogginess. Blood samples were drawn within 48 hours of admission for serum PSA and high sensitivity C-reactive protein (hs-CRP) estimation, and serum was stored at -80°C for batched analysis. Since DRE may lead to an increase in serum PSA levels, blood samples were drawn before performing DRE. Serum PSA levels were estimated in duplicate using a two-site immune-enzymatic sandwich assay that uses a mouse monoclonal anti-PSA antibody (Cat. No. 37200, Hybritech Prostate Specific Antigen, Beckman Coulter, Fullerton, CA) as described for the National Health and Nutrition Examination Survey 2001-2002[9]. Serum hs-CRP was estimated in duplicate using a solid phase direct sandwich assay which uses a monoclonal antibody (Cat. No. CR120C, Calbiotech. Inc., El Cajon, CA) as per the manufacturer's instructions. All patients underwent ultrasonographic examination of kidney, ureter and bladder. As soon as the patients became clinically stable, a transrectal ultrasound (TRUS) examination of the prostate and seminal vesicles was performed using Famio 8 SSA-530A (TOSHIBA), PVQ 641V 6 MHz probe by a urology senior resident. We collected data on the antibiotic regimen started, duration of therapy and clinical course during hospital stay.

At the first follow-up assessment after one month of treatment completion, serum PSA estimation was done in all patients. In those with persistent fever or urinary tract symptoms, urine dipstick leukocyte esterase test and microscopic examination were done. In those with evidence of significant pyuria, urine culture was repeated. At the second follow-up visit after three months of treatment completion, clinical evaluation and repeat measurements of serum levels of PSA and hs-CRP were done. TRUS was also repeated to re-assess the size of prostate and to assess resolution or persistence of inflammation. A baseline serum PSA level above 97.5th percentile of decade-specific serum PSA levels in healthy Indian men was considered to be elevated. We calculated this upper limit cut-off based on a previous study of serum PSA levels among 1300 healthy adult Indian men[10]. We used the decade-specific mean and standard

deviation (SD) of PSA values and calculated the 97.5th percentile as mean + 1.96 SD. We defined prostatic involvement as per the criteria suggested by Ulleryd *et al*[3]. A reduction of serum PSA by >25% irrespective of the initial PSA level, and/or a decrease in prostatic volume by >10% between the acute phase and the follow-up after 3 months was taken as evidence of prostatic involvement.

Sample size calculation

Assuming that 80% of patients would have evidence of prostatic involvement[3], 64 patients were required to estimate this proportion with 10% absolute precision.

Statistical analysis

We summarized categorical variables as n (%) and continuous variables as mean±SD or median (IQR) as appropriate. We applied the Wilcoxon signed rank test to assess the change in serum PSA and serum hs-CRP levels at three months compared to baseline. We performed the Friedman test to analyze the trend of serum PSA at admission, one month and three months. We applied the Wilcoxon rank sum test to compare baseline serum PSA and change in serum PSA levels at three months between patients with and without clinical features suggestive of prostatic involvement. We tested the correlation between baseline serum PSA levels and fall in its levels by three months and that between baseline serum PSA levels and the change in serum hs-CRP levels by three months using Spearman's rank correlation. All analyses were performed using the statistical software package Stata/IC 12.1 for Windows, StataCorp LP, College Station, Texas, USA. All tests were two-sided, and P <0.05 was considered statistically significant. We used GraphPad Prism version 8.3.0 for Windows, GraphPad Software, San Diego, California USA for graphical summaries.

Results

Between July 2016 and May 2018, we screened 91 men with a diagnosis of fUTI and included 64 patients; 50 patients completed follow-up assessments at one month and three months. Figure 1 depicts the flow of subjects through the study. Clinical and laboratory characteristics of the study subjects at baseline are summarized in Table 1. Notably, 16(25%) of 64 patients had presented with obstructive urinary symptoms and 25 (39%) patients ad prostatic tenderness on DRE.

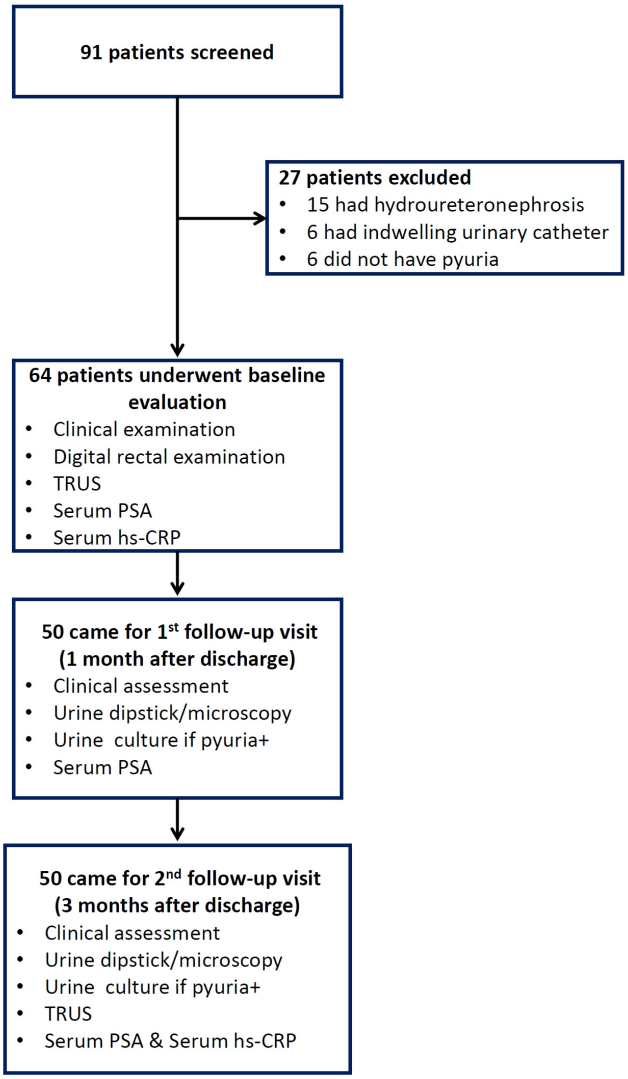

Figure 1. Flow of participants through the study. TRUS, transrectal ultrasound; PSA, prostate-specific antigen; hs-CRP, high sensitivity C-reactive protein.

Mean duration of fever was 6.7±4.4 days; 15 (23%) of 64 patients had received antibiotics prior to study enrollment. Using a strict diagnostic criteria of fever, dysuria, urinary retention and prostatic tenderness on DRE, eight (12%) of 64 patients could be classified as cases of ABP. Urine culture was sent prior to the first dose of antibiotic after admission in 45 (70%) of 64 patients. *Eschericia coli* was the major uropathogen, isolated in 25 (86%) of these 45 patients.

Antibiotic therapy

Empirical antibiotic regimens used in the study population (N=64) were ceftriaxone in 28 (44%), amikacin in 21 (33%), a combination of ceftriaxone and amikacin in seven (11%), cefaperazone/sulbactum in three (5%), a combination of piperacillin/tazobactum and amikacin in three (5%) patients and meropenem in one (2%) patient. A patient with *Candida tropicalis* fungemia and prostatic abscess was treated with fluconazole for 28 days. Modification of the empirical regimen based on susceptibility was done in six (9%) patients. Mean duration of antibiotic therapy was 8.6±3.6 days.

Follow-up assessments and UTI recurrence

Of the 64 patients included, 50 patients came for first follow-up visit after one month of treatment completion. Among them, persistent lower urinary tract symptoms (LUTS) were present in seven (14%) patients. One of them (patient 1), who had fungal prostatic abscess at initial admission, gave a history of recurrent fever. He had significant microscopic pyuria and urine culture showed significant growth of *E. coli*, which was susceptible to

Table 1. Clinical, imaging and laboratory features at admission.

Characteristic	Frequency (n=64)
Age in years, median (IQR)	53(45-60)
Past history of UTI, n(%)	6(9)
Hypertension, n(%)	7(10)
Diabetes, n(%)	23(36)
Chronic kidney disease	8(12)
Co-morbid conditions[a], n (%)	11(17)
Clinical features	
Fever, n(%)	64(100)
Dysuria, n(%)	64(100)
Frequency, n(%)	20(31)
Urgency, n(%)	2(3)
Hematuria, n(%)	1(1.5)
Lower abdominal pain, n(%)	52(81)
Painful ejaculation, n(%)	3(5)
Vomiting, n(%)	2(3)
Retention of urine, n(%)	16(25)
Renal angle tenderness, n(%)	37(58)
Hypotension, n(%)	6(9)
Digital rectal examination findings	
Normal, n(%)	34(53)
Tender and enlarged prostate, n(%)	8(12)
Tender prostate, n(%)	17(27)
Enlarged prostate, n(%)	5(8)
Transabdominal ultrasound findings	
Normal findings	13(20)
Cystitis	42(66)
Pelvicalyceal splitting	27(42)
Bilateral contracted kidneys	5(8)
Renal cysts	5(8)
Renal Stones	1(2)
Ependymal calcification	1(2)
Orchitis	1(2)
Congenital anomaly (duplex kidney)	1(2)
Mild hydroureteronephrosis	1(2)
Laboratory parameters	
Total leukocyte count (cells/μL), mean±SD	14599±11027
Serum creatinine at admission (mg/dL), median(IQR)	1.7(1.1-4.5)
Positive urine dipstick leukocyte esterase, n(%)	64(100)
Urine microscopy pus cells >5 cells/hpf	51(80)
Positive urine culture, n(%)	29(45)
Positive blood culture (N=31), n(%)	12(39)

a = co-morbid conditions include coronary artery disease, malignancy, chronic liver disease, cerebrovascular accident.

UTI, urinary tract infection; IQR, interquartile range; SD, standard deviation; hpf, high-power field.

amikacin. He was re-admitted and was treated with amikacin for seven days. Of the remainder, two patients had significant microscopic pyuria, while four did not. Urine cultures in the two patients with pyuria showed *Klebsiella spp* in one patient (patient 2; treated with nitrofurantoin on ambulatory basis). The third patient's (patient 3) urine culture was contaminated, and a repeat culture was sterile. Since his LUTS improved significantly with increased fluid intake, he was not treated with antibiotics.

The same set of 50 patients attended the three months follow-up. Of note, the three patients (patient1, 2 and 3) who had LUTS and microscopic pyuria during first follow-up visit continued to be symptomatic at this visit too, although none was febrile. They continued to have significant pyuria at this visit. While the repeat urine culture of patient 1 was sterile, patients 2 and 3 had significant bacteriuria, the organisms were different from previous cultures (*Enterobacter spp and Enterococcus spp*, respectively). No antibiotic therapy was prescribed in these three patients at this juncture. They were advised to maintain good hydration. All three patients had significant resolution of symptoms subsequently. Details of these patients are presented in Table 2.

Temporal trends of serum PSA and hs-CRP

At admission, 24 (38%) of 64 patients had elevated serum PSA values. Among the 50 patients who followed up, a significant decrease in serum PSA levels compared to the baseline was noticed at 3 months (Table 3). The fall in serum PSA levels at 3 months was strongly correlated to the baseline serum PSA value (Spearman's rho 0.93; P <0.001; Figure 2, panel B.) Of the 50 patients, 47 (94%) had prostatic involvement as per the pre-defined criteria based on significant change in serum PSA levels. This also included 29 patients whose baseline serum PSA was not elevated.

Serum hs-CRP levels also decreased significantly at three months compared to baseline (Table 3, Figure 3). There was no

Table 2. Details of three patients who were symptomatic on follow-up.

Characteristic	Patient 1	Patient 2	Patient 3
Diabetes	Yes	No	Yes
Past history of UTI	No	No	No
Urinary retention at presentation	Yes	Yes	Yes
Hypotension at presentation	Yes	No	No
Transabdominal ultrasound	Normal	Cystitis	Cystitis
Digital rectal examination	Enlarged and tender prostate	Tender prostate	Tender prostate
Duration of antimicrobial therapy	28 days	7 days	7 days
TRUS findings during index hospitalization	Prostatic abscess	Normal	Normal
Serum PSA at admission, one month and three months follow-up, ng/mL	5.7, 0.55, 0.55	1.9, 1.1, 0.95	2.55, 1.0,1.0
Serum hs-CRP at admission and at three months follow-up, mg/dL	2.2,0.49	1.9, 0.1	3.2,0.13

UTI, urinary tract infection; TRUS, transrectal ultrasound; PSA, prostate-specific antigen; hs-CRP, high sensitivity C-reactive protein.

Table 3. Serum PSA and hs-CRP levels and TRUS findings at admission and follow-up.

Variable	All recruited patients at admission, N=64	Patients with follow-up completed, N=50			
		Admission	1 month	3 month	*P* value
Serum PSA, ng/mL, median (IQR)	2.15(1.18-3.02)	1.95(1.15-2.55)	1.1(0.5-1.8)	0.43(0.3-1)	<0.001
Serum hs-CRP, mg/dL, median(IQR)	2.23 (1.85-2.75)	2.26(1.81-2.75)	--	0.41(0.16- 1.52)	<0.001
TRUS findings					
Prostate volume in mL, median (IQR)	25.4(18.9-34)	24.1(18.72-34.39)	--	21.6(17.7-29.3)	<0.001
Normal, n(%)	38 (59)	26(52)	--	37(74)	NA
Benign prostatic enlargement, n(%)	5(8)	3(6)		3(6)	
Focal hypoechogenicity, n(%)	6(9)	6(12)	--	5(1)	NA
Nodules, n(%)	2(3)	1(2)	--	--	NA
Abscess, n(%)	1(2)	1(2)	--	--	NA
Calcifications, n(%)	13(20)	13(26)	--	13(26)	NA
Seminal vesicle involvement, n(%)	1(2)	1(2)	--	--	NA

PSA, prostate-specific antigen; hs-CRP, high sensitivity C-reactive protein; TRUS, transrectal ultrasound; IQR, interquartile range

correlation between serum PSA levels and hs-CRP levels either at baseline or at three months. The change in serum PSA levels over 3 months had no correlation with the change in serum hs-CRP levels (Spearman's rho 0.19; *P*=0.188).

TRUS findings during hospitalization and at three months follow-up

TRUS was done in 64 patients at baseline, within two (2–4) days of hospitalization. There were no procedure-related

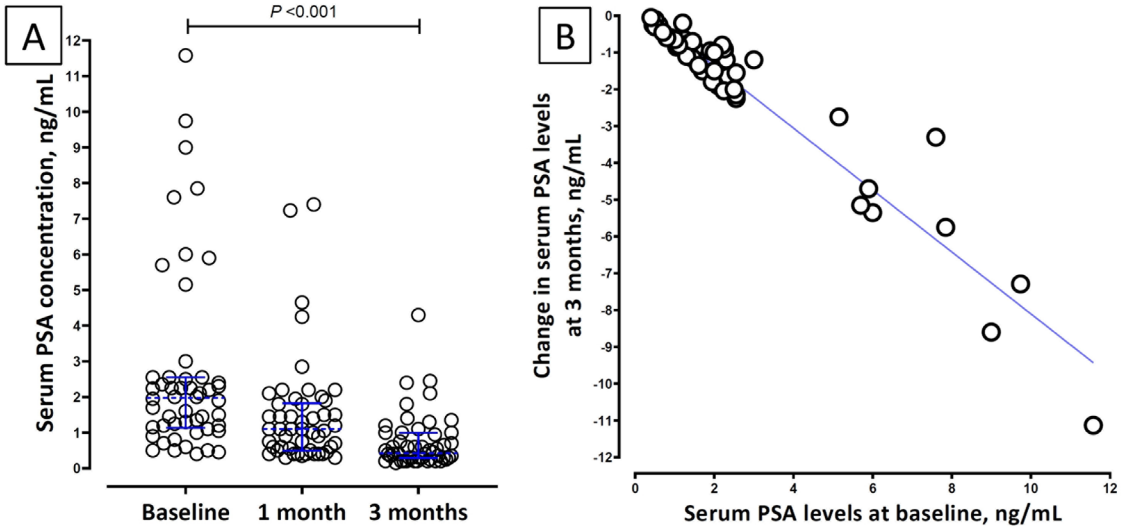

Figure 2. Panel **A**: Dotplot of serum prostate-specific antigen (PSA) levels at baseline, one month and three months of follow-up. Dotted blue lines across the data points depict the median and the error bars depict interquartile range. Panel **B**: Correlation between baseline serum PSA level and the change in PSA levels at three months.

complications. The most significant finding was the presence of prostatic abscess in one patient. Other findings on TRUS are presented in Table 3. Follow-up TRUS examination was done in 50 patients, 95±7 days after hospital discharge. Of the six patients who had focal hypoechogenicity at admission, three continued to have the finding at three months, while new hypoechogenic lesions were noticed in two other patients. However, none of the patients who had these lesions were symptomatic at three months.

A decrease of in prostatic volume ≥10% was observed in 24 (48%) patients. The change in serum PSA levels at three months did not correlate with change in prostatic volume.

Association of baseline and change in serum PSA levels by three months with clinical features

Serum PSA levels at baseline did not differ significantly between patients with/without clinical features suggestive of prostatic involvement such as urinary retention, lower abdominal pain, prostatic tenderness on DRE or a possible diagnosis of ABP. Similarly, none of these clinical features were associated with the change in serum PSA levels compared to the baseline (Table 4).

Discussion

We found that most men with fUTI requiring hospitalization had elevated serum PSA levels and nearly half of them had a decrease in prostatic volume on follow up. However, only a handful of them had clinical findings suggestive of prostatic involvement, and recurrence following treatment was uncommon.

Our findings are in agreement with the seminal study by Ulleryd *et al.*[3]. Although there are a few more studies on PSA levels in men with fUTI, these studies had enrolled patients with ABP[11,12]. The median (IQR) serum PSA levels at admission in our patients was 2.15 (1.18–3.02) ng/mL, which is lower compared to the study by Ulleryd *et al.*, which was 14 (range 0.54–140) ng/mL. We used a chemiluminescent immunoassay method, while Ulleryd *et al.* used a monoclonal fluoroimmunoassay. While mild assay-related variations are possible, the main reason for lower PSA levels in our study could be because of ethnic variations in PSA levels. Studies from India show that the mean serum PSA values in Indian men are lower compared to the Western population[13–15].

Conventionally, elevated PSA levels and a change in prostatic volume have been proposed as definitive evidence of prostatic involvement in men with fUTI[3,6]. Based on this premise, often it is contended that fUTI in men should be treated with antibiotics for a duration of at least two weeks. However, interpreting changes in PSA levels and prostatic volume as reliable evidence of 'prostatitis' is questionable. ABP is a clinically defined entity classically characterized by fever, systemic symptoms, pelvic pain and urinary tract symptoms such as dysuria, urinary frequency, and urinary retention[16]. Although it is known that PSA levels

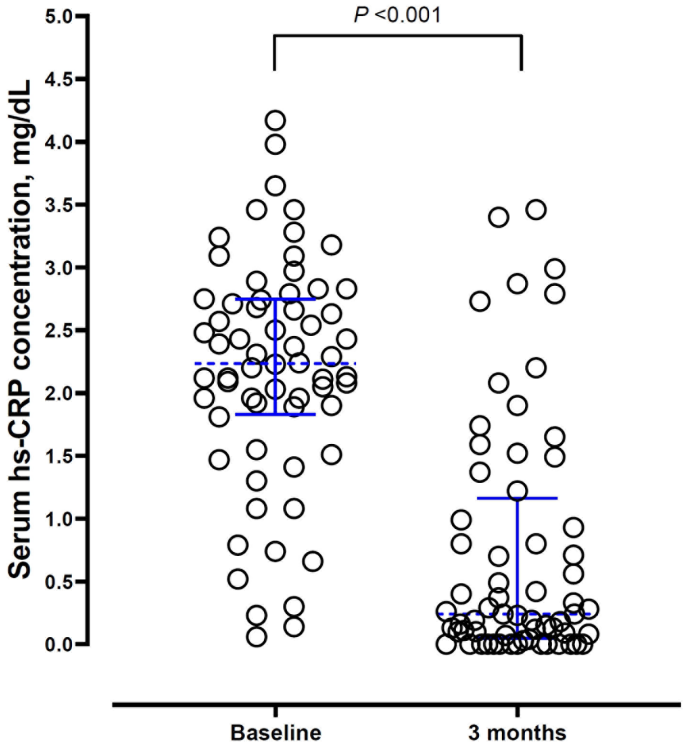

Figure 3. Dotplot of serum high sensitivity C-reactive protein (hs-CRP) levels at baseline and at three months. Dotted blue lines across the data points depict the median and the error bars depict interquartile range.

become elevated in men with ABP, the converse may not be true. Our findings indicate that it might be fallacious to equate pauci-symptomatic elevation of serum PSA levels as definitive evidence of prostatitis due to following reasons.

First, only a minority of patients with such changes actually had clinical findings to suggest prostatic involvement, and the PSA levels and prostatic volume changes were not related to prostatic symptoms. Second, we did not find a correlation between hs-CRP levels and the elevation in PSA levels and the change in prostatic volume. Notably, Ulleryd *et al.* also did not find a correlation between elevated serum PSA and markers of systemic inflammation. Third, despite the fact that 80% of patients were treated with antibiotics for seven days duration, recurrence of UTI was uncommon. Thus, while we confirm the findings that transient elevations in PSA levels and prostatic volume are very common in men with fUTI, we disagree with the interpretation of the clinical significance of these subclinical changes. It is quite possible that the elevated PSA levels indicate a physiological response to bacterial infection rather than indicating a pathological disease process. Townes *et al.* found that epithelial expression and release of PSA was increased by *E. coli* challenge[17]. A few other studies also show that elevated PSA levels represent an enhanced prostate innate host defence[18,19]. Serum PSA levels also rise during episodes of sexually transmitted infections and may remain elevated for several months after effective antibiotic therapy[20]. Other non-genitourinary infections like infectious mononucleosis and chikungunya also cause elevated serum PSA levels[21,22]. It is possible that elevated PSA level is a non-specific response to systemic inflammation caused by prostate cell damage and increased vascular permeability.

We found the presence of focal hypoechoic areas in prostate in a small proportion of patients, the significance of which is unclear — these patients also had good response to treatment and none had LUTS on follow up. Horcadaja *et al.* observed hypoechoic lesions in about 25% of patients with ABP[23]; these lesions persisted in about one-third of patients after antibiotic therapy for one month.

The practical application of clinically distinguishing fUTI from ABP is mainly to decide on the choice and duration of antibiotics. It would be fallacious to justify the need for prolonging the antibiotic treatment based solely on biochemical and TRUS

Table 4. Comparison of baseline and change in PSA levels at three months in patients with and without clinical features of prostatic involvement.

Clinical finding	Baseline serum PSA level, ng/mL		*P* value	Change in serum PSA level at three months, ng/mL		*P* value
	Present	Absent		Present	Absent	
Urinary retention	2.07 (1.45 to 4.75)	2.15 (1.03 to 2.9)	0.40	-1.35 (-2.04 to -0.9)	-1 (-0.2 to -0.65)	0.51
Lower abdominal pain	2.0 (1.05 to 3.05)	2.4 (1.45 to 3)	0.29	-0.95 (-2.0 to -0.65)	-1.2 (-2.25 to -1.1)	0.91
Prostatic tenderness	2.1 (1.05 to2.7)	2.2 (1.2 to 4.9)	0.63	-1.35 (-2.07 to -0.6)	-1.05 (-2 to -0.7)	0.96
Possible ABP[a]	2.2 (1.57 to 4.2)	2.15 (1.13 to 3.02)	0.61	-1.5 (-4.7 to -0.95)	-1.05 (-0.2 to - 0.67)	0.39

All data presented as median (IQR), [a]Defined as presence of fever, dysuria, urinary retention and prostatic tenderness on DRE

PSA, prostate-specific antigen; ABP, acute bacterial prostatitis; IQR, interquartile range; DRE, digital rectal examination

changes which might possibly suggest prostatic involvement. While clinicians generally agree on the need to treat patients with ABP for at least two weeks, it needs to be pointed out that this duration is not based on good quality evidence[24]. In addition, considerable heterogeneity exists in the diagnosis and management of ABP among various clinical departments[25]. Even though a shorter duration of antibiotics was associated with an increased risk of recurrent prostatitis in observational studies, it could be because those patients had clinically manifest ABP and not just biochemical and/or ultrasonographic changes[26]. Indeed, even in ABP, some experts believe that the role of shorter treatment duration needs to be explored[27]. This is a very important aspect since longer treatment durations have been paradoxically associated with increased late recurrences of UTI in the outpatient setting[28]. In addition, longer antibiotic treatment durations do not augur well with the principles of antibiotic stewardship[29].

Very few clinical trials have addressed the issue of optimal treatment duration for fUTI in men without features of ABP. A recent trial from the Netherlands found that shorter duration resulted in lower clinical cure rates at short term in men[30]. Prostatic involvement was attributed as a possible reason for this. However, clinical cure at 70-84 days did not differ between genders, and shorter treatment did not result in more recurrence in men on long term. Another smaller trial from India comparing non-fluoroquinolone antibiotic therapy for seven or 14 days found no difference in re-treatment rates between males and females[31]. Average antibiotic treatment duration in the present study was less than 10 days. Yet, we did not find significant short-term recurrence of fUTI in them.

Possible limitations of our study are: i) it would have been more informative if we had longer follow-up and assessment for chronic prostatitis in the study population; ii) measurement of prostatic volumes potentially could have been affected by inter-observer variability; and iii) we did not collect data on glandular vascularity, which could indicate the presence of inflammation[32].

Conclusions

In conclusion, increase in serum PSA levels and certain ultrasonographic findings, which might possibly indicate subclinical prostatic involvement, were very common among men with fUTI. However, the clinical significance of these changes is uncertain.

Data availability

Underlying data

Figshare: Prostatic involvement in male UTI. https://doi.org/10.6084/m9.figshare.12286865.v2[33]

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Open Peer Review

Current Peer Review Status: ✔ ?

Version 2

Reviewer Report 03 November 2020

https://doi.org/10.5256/f1000research.30053.r73747

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Aneesh Basheer
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[2] Cochrane Neuromuscular Diseases group, London, UK

Many thanks for responding patiently to my comments.
The revised version has more clarity of methods and the primary research question.
The issue of age related variability of PSA levels has also been addressed satisfactorily.
However, the discussion still begins with a statement that it is difficult to accept based on data presented. It states that "We found that most men with fUTI requiring hospitalization had elevated serum PSA levels and nearly half of them had a decrease in prostatic volume on follow up", although in the response to review comments the authors mention that some modification has been made.
Even if the said modification is considered, it would be difficult to accept the explanation of high PSA levels based on a significant fall in levels at 3 months. I would strongly urge authors to interpret the baseline PSA as it is, while mentioning that there was a significant drop at 3 months. I am disinclined to believe that such drop is indirect evidence of a high baseline PSA when actually the data pretty obviously shows PSA levels well within age specific cut offs with some outliers.
Apart from this I find the revised paper high in validity and methodological soundness.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Infectious diseases, tropical medicine, hematology, evidence based medicine, medical education

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 04 Nov 2020

Surendran Deepanjali, Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER)., Dhanvantri Nagar, India

Version 2: Response to Dr Aneesh Basheer

We thank Dr. Basheer for finding the revisions satisfactory, except for the beginning statement in the Discussion section. We agree with Dr Basheer that the statement that "most men with fUTI requiring hospitalization had elevated serum PSA levels" might not be factually accurate. We are happy to modify the first sentence in Discussion section as "We found that about a third of men with fUTI requiring hospitalization had elevated serum PSA levels at presentation, and most men with fUTI requiring hospitalization had at least 25% decrease in serum PSA level at 3 months." We hope that Dr. Basheer finds this modification satisfactory.
Thank you.

Competing Interests: None to disclose

Reviewer Report 28 October 2020

https://doi.org/10.5256/f1000research.30053.r73746

Veeravan Lekskulchai
Department of Pathology, Faculty of Medicine, Srinakharinwirot University, Bangkok, Thailand

The authors have corrected their article and answered my question clearly. I have no further comments to make.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Clinical Pathology, Clinical Chemistry, Clinical Toxicology

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 1

Reviewer Report 17 August 2020

https://doi.org/10.5256/f1000research.26580.r68790

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Aneesh Basheer
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Rationale and research question
The authors submit evidence from literature that supports involvement of the prostate in a high proportion of men with febrile UTI. These studies primarily used surrogate markers to identify prostate involvement such as elevated prostate specific antigen (PSA) or increased prostate volume by ultrasonography. When acute bacterial prostatitis (ABP) is diagnosed, treatment with appropriate antibiotics for 2 to 4 weeks would be needed. ABP typically presents with pelvic pain and voiding symptoms. If the prostatic involvement in febrile UTI is a subclinical ABP, this would need similar treatment.
The authors tried to determine whether this subclinical involvement (evidenced by elevated PSA and prostate volume) had any association with short term UTI recurrence and clinical findings.
The research question is not specified anywhere in the paper. It is suggested that a clear research question be added at the end of the introduction.

Methods:
The authors have used a prospective cohort design to address the issue. This is generally the ideal method to study and correlate variables longitudinally. The methods section is well written and describes the recruitment and follow up in great detail.
The absence of an a-priori comparison group is a weakness, albeit minor. Instead the authors chose to analyze sub-groups from the single cohort of men with febrile UTI – those with features suggestive of clinical prostatitis and those without. A much better and internally valid design would have been the recruitment and follow up of 2 different groups in a similar manner.

Results:
The introductory paragraph on results has data pertaining to calculations based on 64 original participants, 50 finally available cases and a subgroup of cases where cultures were taken prior to antibiotics. The percentages provided therefore could confuse readers and hence it is suggested that authors clearly reframe the sentences to indicate the population from which these numbers and percentages were obtained.
There were 25 patients with prostate tenderness; however, authors mention that only 8 could be classified as Acute bacterial prostatitis. It is not clear then under what banner, the remaining 17 patients fall?

Discussion:
The authors state that most men with febrile UTI had elevated PSA. From the results it is not clear what cut-off was used to determine elevated PSA. Since PSA cut offs are generally age based, it would also be interesting to note the effect of age of the cases on the PSA levels. A regression analysis could probably provide useful information in this regard. Moreover, the results section states that only 14 (22%) of the participants had PSA levels more than 4 ng/mL. The median PSA of

the patients was 2.15 which is also well within normal ranges for the lowest age groups used for PSA cut offs. This disparity between results and the discussion section needs to be clarified.
Authors noted a statistically significant drop in the PSA levels at baseline and at 3 months. Further, 94% of patients had more than 25% drop which was the predefined significant change.
The predefined significant change occurred. However, the baseline PSA itself was not high. The authors need to discuss this in their limitations. It is possible that the 25% reduction considered by authors may not be the "minimal clinically important difference". The other possibility is that these effects have been affected by the low baseline prostate involvement that was presupposed as 80% for sample size calculation.

Overall comments: Well written except for minor modifications suggested.

Is the work clearly and accurately presented and does it cite the current literature?
Yes

Is the study design appropriate and is the work technically sound?
Partly

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?
Partly

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Infectious diseases, tropical medicine, hematology, evidence based medicine, medical education

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 03 Oct 2020

Surendran Deepanjali, Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER)., Dhanvantri Nagar, India

Response to Dr Aneesh Basheer

We thank Dr Basheer for the very constructive comments, and we have modified the

manuscript incorporating his suggestions. Please find below a point-by-point response to Dr Basheer's comments and queries.

Comment: *Rationale and research question. The authors submit evidence from literature that supports involvement of the prostate in a high proportion of men with febrile UTI. These studies primarily used surrogate markers to identify prostate involvement such as elevated prostate specific antigen (PSA) or increased prostate volume by ultrasonography. When acute bacterial prostatitis (ABP) is diagnosed, treatment with appropriate antibiotics for 2 to 4 weeks would be needed. ABP typically presents with pelvic pain and voiding symptoms. If the prostatic involvement in febrile UTI is a subclinical ABP, this would need similar treatment. The authors tried to determine whether this subclinical involvement (evidenced by elevated PSA and prostate volume) had any association with short term UTI recurrence and clinical findings. The research question is not specified anywhere in the paper. It is suggested that a clear research question be added at the end of the introduction. The research question is not specified anywhere in the paper. It is suggested that a clear research question be added at the end of the introduction.*

Response: We thank Dr Basheer for summing up our study's rationale very thoroughly. As per your suggestion, we have now explicitly spelt out the aim of our study at the end of Introduction. We write " We, therefore, conducted the present study to answer the following research questions — i) What is the frequency of prostatic involvement in men with fUTI, and ii) Is prostatic involvement associated with recurrence of UTI?"

Comment: Methods**:** *The authors have used a prospective cohort design to address the issue. This is generally the ideal method to study and correlate variables longitudinally. The methods section is well written and describes the recruitment and follow up in great detail.*

Response: We thank Dr Basheer for the encouraging comments.

Comment: *The absence of an a-priori comparison group is a weakness, albeit minor. Instead the authors chose to analyze sub-groups from the single cohort of men with febrile UTI – those with features suggestive of clinical prostatitis and those without. A much better and internally valid design would have been the recruitment and follow up of 2 different groups in a similar manner.*

Response: We would like to clarify that the definition of prostatic involvement was specified *a priori* in our study protocol. We had given in the Methods section of version 1 that "As defined by Ulleryd et al [3], a fall of ≥25% in serum PSA levels at 3 months, and a decrease in prostatic volume of ≥10% at 3 months were considered significant." However, for the sake of better understating, we have re-worded this as "We defined prostatic involvement as per the criteria suggested by Ulleryd et al [3]. A reduction of serum PSA by >25% irrespective of the initial PSA level, and/or a decrease in prostatic volume by >10% after 3 months was taken as evidence of prostatic involvement." By nature of this definition, it is not possible to classify patients upfront at inception into those with and without prostatic involvement, as suggested by Dr Basheer. However, we agree with Dr Basheer that these patients could be followed up beyond 3 months to ascertain long term outcomes, which was not done in our study.

Comment: Results:*The introductory paragraph on results has data pertaining to calculations*

based on 64 original participants, 50 finally available cases and a subgroup of cases where cultures were taken prior to antibiotics. The percentages provided therefore could confuse readers and hence it is suggested that authors clearly reframe the sentences to indicate the population from which these numbers and percentages were obtained.

Response: We thank Dr. Basheer for pointing this out. We have now modified the introductory paragraph taking care that the reference population for the percentages is clearly specified. Also, data presented in Table 3 now clearly demarcate information from all 64 recruited patients at baseline from those 50 in whom complete follow-up is available. Similarly Figures 2 & 3 have been modified to represent data from 50 patients only.

Comment: *There were 25 patients with prostate tenderness; however, authors mention that only 8 could be classified as Acute bacterial prostatitis. It is not clear then under what banner, the remaining 17 patients fall?*

Response: As we had pointed out in the Discussion section, it is known that there is much heterogeneity among clinicians from different disciplines in arriving at a diagnosis of ABP (Reference 24, version 1). While some clinicians might feel that prostatic tenderness alone is sufficient to diagnose ABP in men with fUTI, many physicians might not agree with this. Therefore, to ensure reproducibility we have adopted a classical syndromic definition for ABP in which only those patients with tender prostate as well as urinary retention (which is a voiding symptom) were classified as ABP. We chose this stricter definition to make the clinical diagnosis unambiguous, since we also intended to evaluate whether the diagnosis had any bearing on baseline serum PSA levels and its longitudinal changes (Table 4, version1). While it is quite possible that the remaining 17 patients had a *forme fruste* of ABP, the present study was not designed to answer this question. Moreover, even when the analysis was based on individual symptoms, we did not find any association with serum PSA levels (Table 4).

Comment: Discussion: *The authors state that most men with febrile UTI had elevated PSA. From the results it is not clear what cut-off was used to determine elevated PSA. Since PSA cut offs are generally age based, it*
would also be interesting to note the effect of age of the cases on the PSA levels. A regression analysis could probably provide useful information in this regard. Moreover, the results section states that only 14 (22%) of the participants had PSA levels more than 4 ng/mL. The median PSA of
the patients was 2.15 which is also well within normal ranges for the lowest age groups used for PSA cut offs. This disparity between results and the discussion section needs to be clarified. Authors noted a statistically significant drop in the PSA levels at baseline and at 3 months. Further,
94% of patients had more than 25% drop which was the predefined significant change. The predefined significant change occurred. However, the baseline PSA itself was not high. The authors need to discuss this in their limitations. It is possible that the 25% reduction considered by
authors may not be the "minimal clinically important difference". The other possibility is that these
effects have been affected by the low baseline prostate involvement that was presupposed as 80%

for sample size calculation.

Response: We thank Dr Basheer for drawing our attention to this important aspect of interpretation of serum PSA levels in our study population. We would like to clarify that we stated that serum PSA levels were elevated in most men with febrile UTI, based on the observation that almost 94% of men had a significant fall in serum PSA values at 3 months compared to their baseline value. Following Dr Basheer's suggestion, we have incorporated age-specific cut offs in the revised manuscript to interpret the PSA values at baseline (Please see last paragraph under 'Study procedure' in Version2). It is true that only 38% of patients had a baseline PSA value above the upper limit of their age-specific reference age. We use the 97.5th percentile value as the upper limit of reference range. However, serum PSA values in apparently normal healthy men in a specific age-group could show considerable variability within the reference range. For example, in the age-group 50-59 years the minimum value was 0.06 ng/mL, while the maximum was 5.9 ng/mL. Thus, even if the baseline value was within the reference range, a dynamic fall on follow-up would suggest that the baseline was elevated for a given patient.
Nevertheless, we agree that the statement "We found that most men with fUTI requiring hospitalization had elevated serum PSA levels" could be confusing, and hence we have modified this in Version 2. We have now modified it as "We found that most men with fUTI requiring hospitalization had significant decrease in serum PSA levels at 3 months follow-up indicating an elevated baseline value, and nearly a half of them had a decrease in prostatic volume on follow-up."
As suggested by Dr Basheer, we checked for a linear relationship between age and baseline PSA levels by doing a simple linear regression. However, we did not find a relationship between age and PSA levels (coefficient = 0.017; P = 0.486). Although it is well known that PSA levels increase with age, we did not find such a relationship. Most probably, infection-induced changes in PSA distort and overshadow any such underlying relationship in our dataset. Similar to our findings, Ulleryd et al (reference 3) also did not find a correlation between age and serum PSA levels during episode of fUTI in men.

We hope Dr Basheer finds the modifications satisfactory, and we once again express our gratitude for your suggestions. We would definitely address any other ensuing concerns regarding our manuscript.

Thank you.

Competing Interests: No competing interests to disclose.

Reviewer Report 10 August 2020

https://doi.org/10.5256/f1000research.26580.r68741

Veeravan Lekskulchai
Department of Pathology, Faculty of Medicine, Srinakharinwirot University, Bangkok, Thailand

This work is entitled "Frequency and clinical significance of prostatic involvement in men with febrile urinary tract infection: a prospective observational study" and was written by Arjunlal *et al.* The authors studied chances of having acute bacterial prostatitis in male admitted with urinary tract infection. The manuscript was written appropriately and relevantly. However, I have a few major concerns for this work. First in the Results, though, 64 patients were enrolled and their baseline results were available, 14 of them were not followed up and were excluded after that. Consequently, the baseline results of these 14 patients should be excluded from this work (Table 3, Figure 3). The baseline results should come from 50 patients similar to the results in the next one and 3 months. Another concern is why they used hs-CRP in cases whose inflammation were obviously indicated. They should use CRP level. This point needs an explanation.My minor concern is the use of old references. If possible, they should be replaced by newer ones.

Is the work clearly and accurately presented and does it cite the current literature?
Partly

Is the study design appropriate and is the work technically sound?
Yes

Are sufficient details of methods and analysis provided to allow replication by others?
Yes

If applicable, is the statistical analysis and its interpretation appropriate?
Partly

Are all the source data underlying the results available to ensure full reproducibility?
Yes

Are the conclusions drawn adequately supported by the results?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Clinical Pathology, Clinical Chemistry, Clinical Toxicology

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 03 Oct 2020

Surendran Deepanjali, Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER)., Dhanvantri Nagar, India

Response to Dr. Veeravan Lekskulchai

We thank Dr Lekskulchai for the very helpful and constructive comments. We have tried to address the concerns raised by Dr Lekskulchai and have made modifications in our manuscript accordingly. Please find below a point-by-point response to the comments.

Comment: *This work is entitled "Frequency and clinical significance of prostatic involvement in men with*
febrile urinary tract infection: a prospective observational study" and was written by Arjunlal et al.
The authors studied chances of having acute bacterial prostatitis in male admitted with urinary tract infection. The manuscript was written appropriately and relevantly. However, I have a few major concerns for this work.

Response: We are grateful for the kind compliments. We hope to address the concerns raised by Dr Lekskulchai.

Comment: *First in the Results, though, 64 patients were enrolled and their baseline results were available, 14 of them were not followed up and were excluded after that. Consequently, the baseline results of these 14 patients should be excluded from this work (Table 3, Figure 3). The baseline results should come from 50 patients similar to the results in the next one and 3 months.*

Response: We than Dr Lekskulchai for pointing this out. We have now presented the important baseline variables pertaining to the 50 patients separate from the total 64 recruited patients in Table 3. Also, we have modified Figure 3 accordingly to include data pertaining to these 50 patients only.

Comment*: Another concern is why they used hs-CRP in cases whose inflammation were obviously indicated. They should use CRP level. This point needs an explanation.*

Response: Dr Lekskulchai is correct in pointing out that serum CRP estimation would be better than hs-CRP in patients with obvious inflammation such as febrile UTI. However, a pre-specified follow-up at 3 months was planned in our study, and it was expected that UTI-associated inflammation would have substantially decreased in many patients on follow-up. Since a more sensitive assay would be required to demonstrate this low-grade inflammation with CRP concentrations often below 1.0 mg/dL, we used an hs-CRP assay rather than a CRP assay. Previous studies on subclinical prostatic inflammation have used hsCRP as a biomarker (*Milbrandt M, Winter AC, Nevin RL, et al. Insight into infection-mediated prostate damage: Contrasting patterns of C-reactive protein and prostate-specific antigen levels during infection. Prostate. 2017;77:1325-1334.*).
We are also duty-bound to inform Dr Lekskulchai that the query on the utility of hs-CRP made us look closely at the hs-CRP primary data. We then identified an inadvertent data entry error. We realized that the optical density values of the ELISA read-outs were mistakenly entered as the actual hs-CRP values. We sincerely regret this inadvertent error. We have now uploaded a corrected version of the underlying data set containing the corrected hs-CRP values which can be found at *Deepanjali, Surendran; Thayyil, Arjunlal; Rajappa, Medha; Ramanitharan, Manikandan (2020): Prostatic involvement in male UTI. figshare. Dataset. https://doi.org/10.6084/m9.figshare.12286865.v3*. Accordingly, we also have now

made necessary changes in descriptive data on serum hs-CRP as well as Figure 4. While this error does not change our findings and conclusions, we found that the weak correlation between change in serum PSA levels with change in serum hs-CRP levels was no longer significant when the analysis was repeated using corrected hs-CRP values. We have now provided this information in Version 2.

Comment: *My minor concern is the use of old references. If possible, they should be replaced by newer ones.*

Response: We ran an updated PubMed search using terms “serum PSA AND urinary tract infections”, “serum PSA and acute bacterial prostatitis” and “hs-CRP AND urinary tract infection”. However, we could not find any newer reference related to our manuscript. If Dr Lekskulchai could kindly point out any particular reference/references which needs to be checked for new information, we would be happy to do so.
We sincerely hope Dr Lekskulchai finds our responses satisfactory. We would certainly try to address any further concerns if present.

Thank you.

Competing Interests: No competing interests to disclose.