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The relation between baseline PSA and symptomatic progression in Egyptian BPH patients receiving tamsulosin monotherapy: an exploratory multicentric prospective study

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Abstract

Background: To examine the relation of baseline serum prostatic-specific antigen (PSA) to symptomatic changes in men with benign prostatic hyperplasia (BPH) receiving tamsulosin through its relation to changes in international prostate symptom score (IPSS) and maximum urinary flow rate (Qmax) and the occurrence of acute urine retention (AUR).

Results: We conducted a multicentric prospective cohort study. BPH patients were included from May 2015 till January 2018. We collected IPSS recording, prostate volume (PV) Qmax. After 2 years of medical treatment with tamsulosin 0.4 mg once daily, full initial evaluation was repeated for all patients. Improvement in IPSS and Qmax was recorded and compared to initial PSA levels. Follow-up was aborted for patients who developed AUR. Moreover, the data of AUR patients were recorded and compared to initial PSA levels. The study included 437 Egyptian patients, and 414 patients (94.7%) had symptomatic improvement through the 2 years of follow-up on tamsulosin monotherapy. In total, 23 patients (5.3%) developed AUR during follow-up. There was a significant association between AUR and higher baseline PSA level ($p < 0.001$). On the other hand, statistical analysis showed that there was no significant correlation between baseline serum PSA and the improvement in IPSS ($r = -0.02$, $p = 0.684$) or Qmax ($r = -0.06$, $p = 0.267$). The multivariate analysis showed that baseline PSA and PV were independent predictors for AUR ($p < 0.001$ for both).

Conclusions: There was a significant relation between baseline PSA and incidence of AUR. However, there was no significant relationship between the serum PSA level and symptoms improvement in BPH.

Keywords: Serum PSA, Prostate volume, Lower urinary tract symptoms, Benign prostatic hyperplasia, Maximum urinary flow rate, Tamsulosin

1 Background

Benign prostatic hyperplasia (BPH) is a chronic complex disease that clinically manifests by lower urinary tract symptoms (LUTS). While BPH progresses, the prostate volume (PV) increases, and Qmax decreases. LUT symptoms may deteriorate to the extent of serious clinical outcomes as acute urinary retention (AUR) that usually requires further surgical intervention [1–3].

Unless indicated for surgery, most BPH patients receive medical treatment. Alpha blockers are considered the main prescribed medication. Alpha blockers can decrease the risk of clinical progression including symptomatic deterioration, AUR or surgical interventions, yet this effect is much obvious when alpha blockers are combined to 5ARIs [4, 5].

As for medically managed BPH patients, several authors studied the correlations between the baseline

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prostatic-specific antigen (PSA) and BPH symptoms progression parameters. These BPH parameters included prostate volume, prostate growth, change in Qmax and IPSS, the risk of acute urinary retention (AUR) and required surgical intervention. Moreover, some studies evaluated the relation between the initial PSA and clinical deterioration while on placebo, dutasteride or tamsulosin therapy [4, 6–10].

In our study, we tried to assess the relation between the baseline PSA and symptomatic changes—whether improvement or deterioration—in Egyptian BPH patients treated with tamsulosin monotherapy during 2 years of follow-up.

2 Methods

After obtaining the research ethics board approval, a multicenter prospective cohort study was conducted from May 2015 till January 2018 in all participating institutions in different cities across Egypt. BPH patients presented with LUTS and aged 50 years old or more with no history of previous treatment for BPH were included. We excluded from the start patients with absolute indications for surgical intervention such as: refractory hematuria, recurrent UTI, concomitant bladder stones, second renal insufficiency and inguinal hernia. We did not have a placebo arm in our study for ethical reasons.

After initial evaluation, recruited patients those who did not fulfill the following clinical inclusion criteria were excluded. We excluded those who had urine retention from the start, suspicious DRE, IPSS < 8, serum total PSA level above 4 ng/dl, Qmax > 15 ml/s, and patients with history of previous lower urinary tract intervention.

Before enrollment in the study, we obtained informed consent from all patients after explaining the nature and consequences of the procedure in detail in the patient's own language.

Thereafter, all patients were evaluated at presentation. Evaluation included full medical history with IPSS recording, careful clinical examination including digital rectal examination to exclude patients with hard nodules or asymmetry in the prostate gland. IPSS was considered moderate if it was 8–19 and severe if it was more than 19. Moreover, laboratory investigations including urine analysis, kidney function tests, serum total PSA level were performed. All patients underwent pelvi-abdominal ultrasound for the estimation of prostate volume (PV) and uroflowmetry to record Qmax. Patients were categorized in relation to their PSA and PV. Serum PSA subgroups included < 1.5 ng/ml, 1.5–2.7 ng/ml and > 2.7 ng/ml. PV subgroups were < 40 g, 40–60 g and > 60 g.

Tamsulosin 0.4 mg once daily was prescribed for all patients. Adherence to treatment was ensured at outpatient follow-up visits by directly questioning the patients. After 2 years, full evaluation was repeated. Improvement in IPSS and uroflow was recorded and compared to initial PSA levels. Follow-up was aborted if any patient experienced AUR. Moreover, data of patients who had AUR were recorded and compared to the initial PSA levels. These patients were dropped off from the final evaluation after 2 years.

After 2 years of medical treatment with tamsulosin, patients were interviewed again for a full assessment. The final follow-up at 2 years included IPSS and uroflow. The 2-year change of IPSSs, PV and Qmax were calculated using the following equation $(\text{change} = \text{last value} - \text{baseline value})$. We evaluated the relation between the initial PSA and PV subgroups with IPSS and Qmax changes.

Our primary outcome was to evaluate the relationship between the baseline serum prostatic-specific antigen (PSA) and symptomatic changes in men with moderately severe LUTS due to BPH who received tamsulosin monotherapy. Our secondary outcomes were included to assess the IPSS and Qmax changes in relation to PSA and PV subgroups after 2 year of tamsulosin monotherapy.

Data were coded and entered using the SPSS (Statistical Package for the Social Sciences) version 20. Continuous data were presented as medians and ranges and evaluated using the nonparametric Mann–Whitney test [11]. We presented categorical data into numbers and percentages while assessed using the Chi-square test. We correlated the initial serum PSA value of our patients and the symptoms improvement through the change in values of IPSS and the Qmax of uroflowmetry. Moreover, we correlated the change of IPSSs and change of prostatic size. Correlations were done using Spearman's correlation coefficient [12]. Linear logistic regression was used to detect independent predictors of AUR. *P* values less than 0.05 were considered as statistically significant.

3 Results

We recruited 642 Egyptian patients. All patients had LUTS at presentation. We excluded 205 patients at time of initial evaluation as follows: 16 patients with urine retention, 4 patients had nodules on DRE, 64 patients who had PSA more than 4 ng/ml, 32 patients had IPSS < 8 and 76 patients had Qmax > 15. Moreover, we excluded 10 patients with previous urethral instrumentation and 12 patients who refused to continue participation in the study.

Finally, we were able to recruit 437 patients with a median age of 63 (50–90) years (Fig. 1). Out of these 437 patients, only 23 patients developed AUR. Those 23 patients with AUR were involved in our secondary outcome assessment. The 414 patients whom continued the 2-year follow-up were involved in our primary outcome assessment.

3.1 Clinical findings at presentation (Table 1)

The median prostatic size at presentation was 48 g (23–140). We measured a PV < 40 g in 161 patients (36.8%), PV of 40–60 g in 165 patients (37.8%) and PV > 60 g in 111 patients (25.4%). The IPSS was recorded at presentation for all 437 patients with median score 21 (9–30). In total, 269 patients (61.6%) had severe IPSS and the remaining patients (38.4%) had moderate score. The initial median total PSA was 1.7 ng/ml (0.3–3.9). Forty-four percent (192) of patients had serum total PSA < 1.5 ng/ml, 148 patients (33.9%) had PSA 1.5–2.7 ng/ml, and the remaining 97 patients (22.1%) had PSA 2.7–4 ng/ml. The median Qmax was 9.7 ml/s (5–14.5).

3.2 Clinical findings at 2-year follow-up (Table 1)

Only 414 patients (94.7%) underwent post-treatment evaluation after 2 years of medical treatment. Despite the medical treatment, 23 patients (5.3%) developed AUR during the 2-year follow-up.

After 24 months of medical treatment, the median IPSS of the remaining 414 patients was 13 (7–26). The

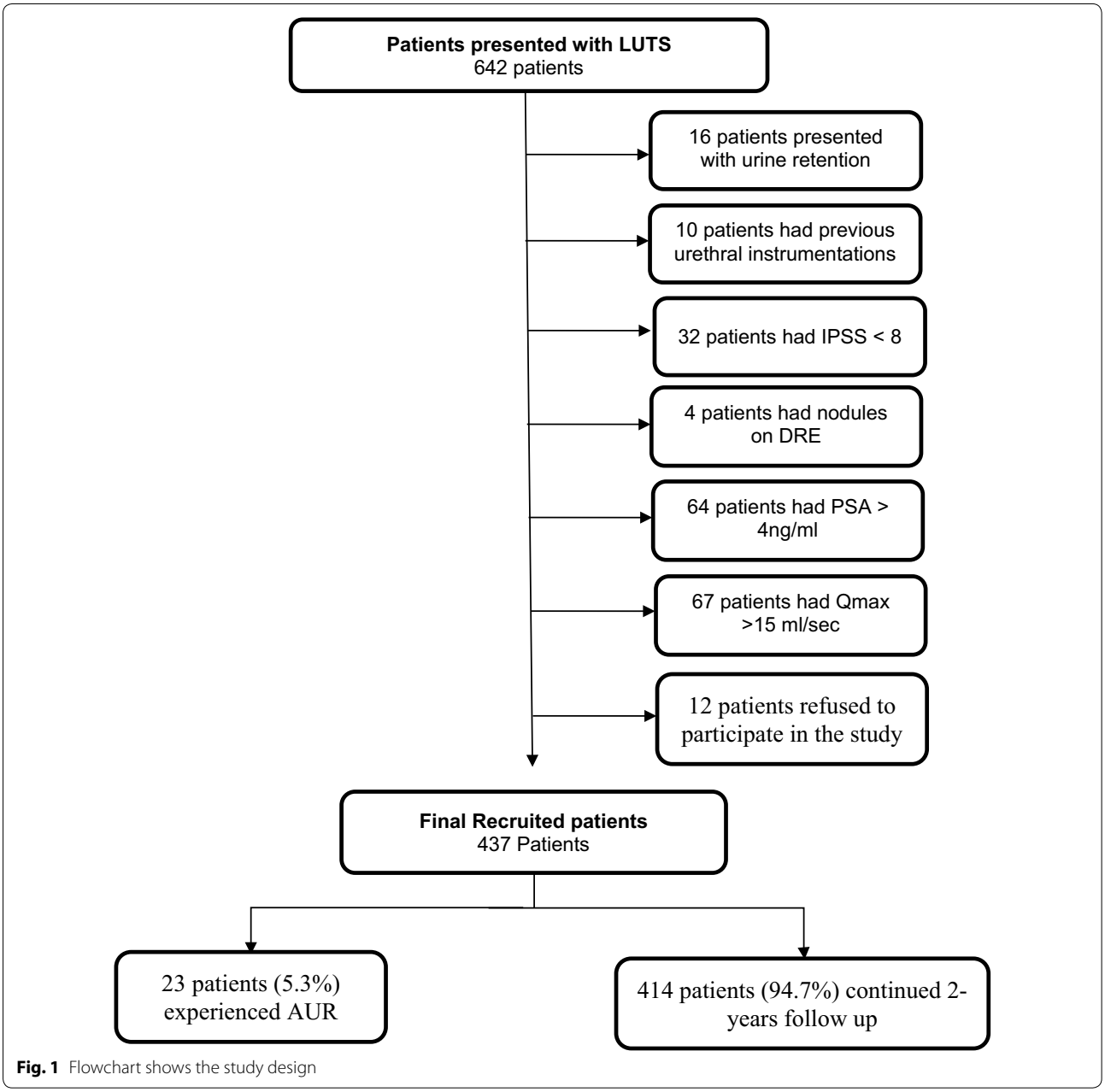

Fig. 1 Flowchart shows the study design

Table 1 Patient's characteristics at presentation and after 2 years of tamsulosin monotherapy

Parameter	Valid *N*	Findings median (range)
At presentation		
Age	437	63 years (50–90)
IPSS	437	21 (14–30)
Prostate volume	437	48 g (23–140)
Qmax	437	9.7 ml/s (5–14.5)
Serum total PSA	437	1.6 ng/ml (3–3.99)
At 2-year follow-up		
IPSS	414	13 (7–26)
Prostate volume	414	53 g (26–165)
Qmax	414	15.6 ml/s (7.5–22)
IPSS change	414	−8 (−20 to 5)
Change of prostate volume	414	6.1 g (−28 to 54)
Qmax change	414	5.55 ml/s (−4.5 to 16)

median IPSS change was −8.5 (− 20 to 5) with a median percentage of change—40% (−68.2 to 11.8). Patients with moderate IPSS had an improvement percentage of −35.3% (−58.8 to 11.8), while those with severe IPSS showed −43.5% (−72 to 5) improvement in their IPSSs ($p<0.001$).

At 2-year follow-up, the uroflowmetry was repeated. The median 2-year Qmax was 16.6 ml/s (7.5–22). The median improvement in Qmax was 5.6 ml/s (−4.5 to 16) with median percentage 58.8% (−34.6 to 320). Patients with initial moderate IPSS had a median Qmax improvement percentage of 57.3% (−22.1 to 320), while those with severe IPSS experienced a 60.1% (−34.6 to 312.6) Qmax improvement ($p=0.8$).

The median prostatic size at 2-year follow-up was 53 g (26–165). The median increase in prostate size was 6.1 g (−18 to 41) with median change percentage 13.7% (−27.3 to 71.9). There was a weak positive correlation between the change of IPSS and the change of prostatic volume ($r=0.15$, $p=0.002$).

There was no significant correlation between serum PSA value and the improvement in IPSS after 2 years of tamsulosin monotherapy ($r=-0.02$, $p=0.684$). The change of PV was not correlated with the initial PSA level ($r=0.08$, $p=0.13$). Moreover, there was no significant correlation between serum PSA value and the improvement in Qmax ($r=-0.06$, $p=0.267$).

After 24 months of tamsulosin monotherapy, there were significant differences among all baseline PSA subgroups regarding the IPSS (Fig. 2a) and Qmax changes (Fig. 2b), whereas the baseline PV subgroups showed significant differences in terms of the IPSS improvement (Fig. 2c) and Qmax (except between < 40 g and 40–60 g) (Fig. 2d).

3.3 AUR patients

Within 24 months of follow-up, 23 patients (5.3%) developed AUR. All patients were indicated to surgical intervention. There was a significant increase in the incidence of AUR with patients with higher baseline PSA level ($p<0.001$).

We noted that those patients who experienced AUR had initial PV nearly double the PV who did not experience AUR ($p<0.001$). Moreover, those patients who experienced AUR had initial PSA greater than twofold the initial PSA of those patients who had no AUR ($p<0.001$) (Table 2).

The univariate analysis showed that age at presentation, initial PSA and PV at presentation were associated with the incidence of AUR, while using a multivariate regression analysis, only initial PSA and PV were independent predictors for AUR (Table 3).

4 Discussion

Tamsulosin is a very popular medication for the management of BPH in our country as it minimally affects the arterial blood pressure and its affordable price [13]. Moreover, it showed long-term tolerability for more than 6 years with 1.3% incidence of orthostatic hypotension [14]. Factors determining the response to medical treatment vary, including genetic factors, geographical distribution and race. Thus, treatment adjustment and response evaluation should be individualized according to the differences among racial and ethnic groups [15]. In the current study, we evaluated the relation between the baseline PSA and symptomatic changes in Egyptian BPH patients treated with tamsulosin monotherapy.

Several clinical trials compared the effect of tamsulosin to dutasteride or combined therapy in terms of PSA, IPSS, Qmax and AUR. These large-scale clinical trials made us think about investigating the unclear relation of baseline PSA to the change of severity of symptoms in BPH patients on tamsulosin monotherapy instead of 5ARIs or combined therapy [4, 6–10]. Therefore, in our study, we preferred to assess PSA relations in tamsulosin monotherapy-treated patients only, especially that tamsulosin monotherapy has fewer side effects and more widely used. In our study, changes in IPSS and Qmax were our key to assess the improvement in the BPH-related LUTS. Despite being studied before, to our knowledge, this is the first study that evaluates the relationship among the Middle Eastern population.

At 2-year follow-up, our patients had a median IPSS change of −8 which is comparable to a mean IPSS change of − 8.5 reported by Narayan and colleagues [14]. In the literature, the median increase in Qmax with tamsulosin monotherapy ranged from 1.6 to 3.5 ml/s [4, 14, 16, 17]. In the current study, the median Qmax improvement was

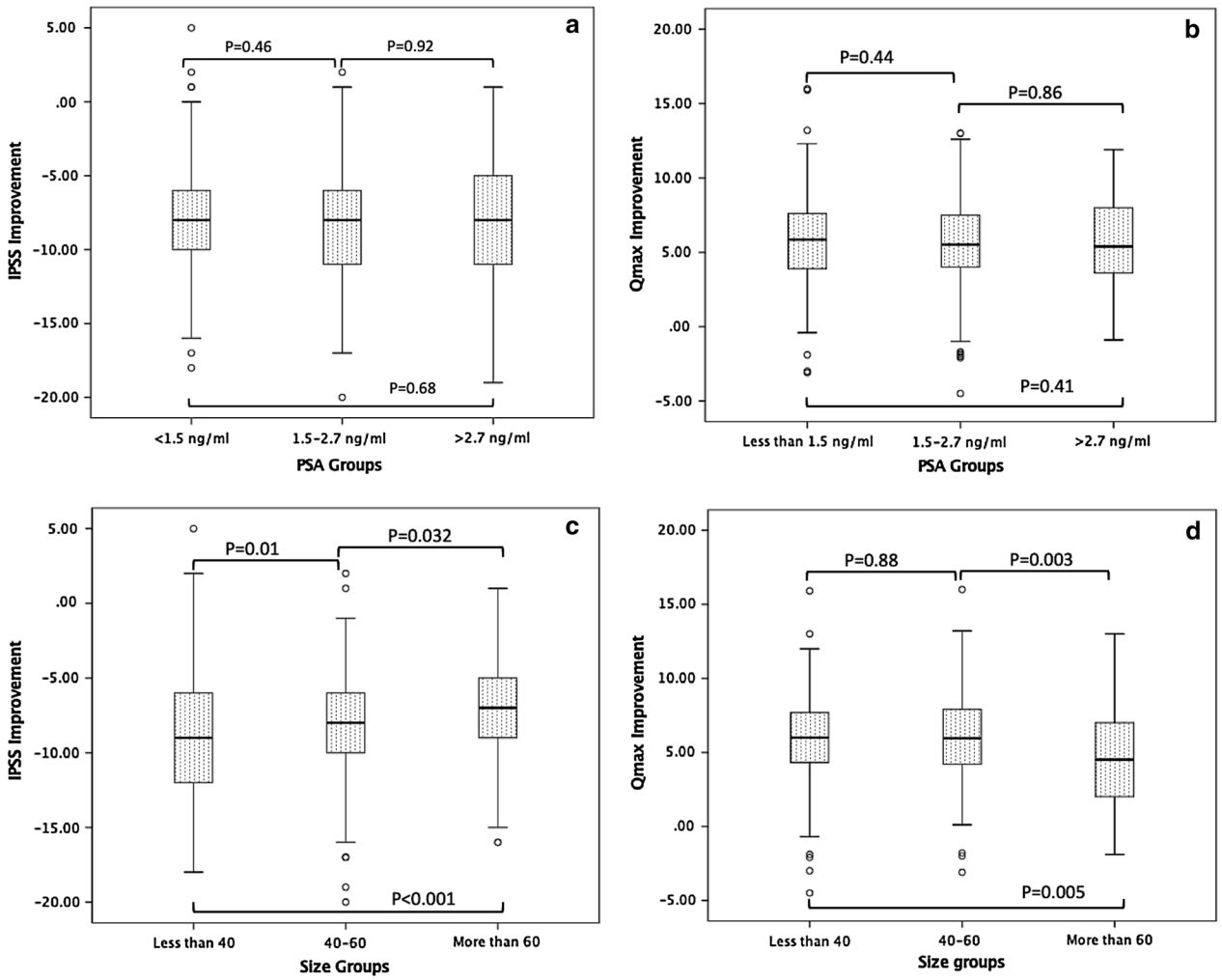

Fig. 2 Boxplot diagrams show **a** IPSS changes in relation to PSA groups, **b** Qmax changes in relation to PSA groups, **c** IPSS in relation to PV groups, **d** Qmax improvement in relation to PV groups

Table 2 Associations between the occurrence of AUR and serum PSA, IPSS, Qmax and prostate volume at initial presentation

Parameters	AUR				*p* value
	Yes		No		
	Median	Range	Median	Range	
Age at presentation years	67	58–81	62	50–90	0.001
IPSS at presentation	19	14–25	21	14–30	0.471
Prostate volume at presentation grams	87	46–140	45	23–135	< 0.001
Qmax at presentation ml/s	9.7	5.6–13.1	9.7	5–14.5	0.596
Total serum PSA at presentation ng/ml	3.33	1.9–3.8	1.5	0.3–3.99	< 0.001

Table 3 Univariate and multivariate regression analysis to detect independent predictors of AUR

Parameters	Univariate analysis			Multivariate analysis		
	HR	CI	*p* value	HR	CI	*p* value
Age at presentation	0.004	0.001–0.006	0.002	− 0.001	− 0.003 to 0.002	0.66
IPSS at presentation	− 0.003	− 0.000 to 0.003	0.34	–	–	–
Prostate volume at presentation	0.004	0.004–0.005	< 0.001	0.065	0.045–0.085	< 0.001
Qmax at presentation	0.002	− 0.008 to 0.012	0.67	–	–	–
Initial PSA	0.083	0.063–0.105	< 0.001	0.004	0.003–0.005	< 0.001

5.55 ml/s. Despite this discrepancy with the literature, this could be explained by racial and ethnic variations, and further studies of the same population are required to evaluate the Qmax improvement after tamsulosin therapy.

After 4 years of follow-up for 4482 men with BPH treated with different medical therapies, Roehrborn et al. [4] found that patients with baseline PSA level of ≥ 1.5 ng/ml had a significant decrease in clinical deterioration on combined therapy or dutasteride monotherapy than on tamsulosin monotherapy. The CombAT study suggested that the effect of the alpha blockers on long-term symptom control was more modest in men with a larger prostate volume or a greater PSA [10]. In the current study, we did not find correlations between the initial PSA and changes of IPSS, PV and Qmax.

As for the risk of AUR, our study results showed that there was a significant relationship between baseline PSA and incidence of AUR and this goes with what the literature expected. For example, Roehrborn et al. studied the baseline PSA relations to prostate growth, the risk of AUR and risk of surgical intervention in placebo-treated patients. They concluded that the baseline PSA was a strong predictor of prostate growth and AUR [6].

The incidence of AUR in our study was 5.3%. Our AUR incidence is similar to Schulman and co-authors report who had an incidence of 4.5% in patients receiving tamsulosin monotherapy for up to 4 years [17].

Some authors studied the baseline PSA relations with the prostate growth, the occurrence of AUR and risk of surgical intervention in placebo-treated patients and concluded that baseline PSA was a stronger predictor of growth of the prostate than age or baseline PV [6, 7]. In our study, we found that PV and PSA were independent predictors for AUR. These findings are similar to the EAU guidelines which elaborate the role of PSA in decision making [18]. Moreover, we found that the median PV and PSA were twice higher than those who did not experience AUR. The ability of PSA to predict prostate growth and risk of AUR may be an important factor when considering management options for BPH. Such use of PSA in addition to the symptoms of BPH provides a more comprehensive approach to predict and further prevent risk factors for BPH-related outcomes.

According to EAU guidelines, combination therapy is better than α1-blockers monotherapy for large prostates management, yet α1-blockers monotherapy is very efficient in improving LUTS and quality of life in BPH in both small prostates and large prostates > 40 ml. Combination therapy is definitely more expensive, and it has clear adverse effects, especially sexual dysfunction with severe impact on quality of life [18]. Thus, using α1-blockers monotherapy was much more suitable for our 2-year follow-up study.

To summarize, results of our study suggest that baseline PSA is not related to the changes in IPSS or Qmax in BPH patients treated with tamsulosin monotherapy, although this relation is confirmed in case of 5ARIs or combination therapies in other studies in the literature. On the other hand, baseline PSA is related to the probability of developing AUR later.

Our study still has some limitations. Only patients treated with tamsulosin monotherapy were evaluated, and we did not include combined therapy with 5ARIs as most of the other studies did. Moreover, we did not plan to compare results to a group of placebo-treated patients; this was due to ethical issues. Moreover, decision making could be influenced by the subjective judgment of participating urologists. Nevertheless, we stick to the recommendation of the EAU guidelines. Lastly, the patient adherence to treatment could be questionable; however, we tried to make sure of that at every follow-up visit through direct questions. More multicenter studies of different countries with comparative arms are warranted to confirm our results.

5 Conclusions

To sum up, in our study for BPH patients with LUTS treated with Tamsulosin monotherapy, there was a significant relation between baseline PSA and incidence of AUR, yet there was no significant relationship between the serum PSA level and the improvement in symptoms of BPH receiving tamsulosin monotherapy. This finding is similar to the recent EAU guidelines which stated the important role of PSA in the prediction of AUR. Further studies may be needed to confirm these results.

Abbreviations
5ARIs: 5 α-reductase inhibitors; AUR: acute urinary retention; BPH: benign prostatic hyperplasia; DRE: digital rectal examination; IPSS: international prostate symptom score; LUTS: lower urinary tract symptoms; PSA: prostate-specific antigen; PV: prostate volume; Qmax: maximum flow rate.

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Authors' contributions
MSE, AYA, ASM, HS, HA and MHA collected the data and drafted the initial manuscript. FZ collected the data and edited the final manuscript. AH drafted the initial manuscript and edited the final manuscript. All authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work. All authors read and approved the final manuscript.

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

Competing interests
The authors declare that they have no competing interests.

Consent for publication
Not applicable.

Ethics approval and consent to participate
The study was approved by the Scientific Research Ethics Committee of Faculty of Medicine—Fayoum University—and was later approved by other participating centers (reference number is not applicable). An informed written consent was obtained from all participating patients after explaining the aim, adverse events and the methodology of the study.

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