

## Presentation and Progression of Benign Prostatic Hyperplasia: A Singapore Experience Profiling Ethnic Differences in a Multiracial Study Cohort

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### Abstract

**Introduction:** While benign prostatic hyperplasia (BPH) incidence has been shown to vary by race and ethnicity, data is lacking among Asians. This study aimed to describe the baseline symptom profile and response to medical therapy in a multiracial Singaporean cohort with BPH. **Materials and Methods:** International Prostate Symptom Score (IPSS), uroflowmetry and prostate specific antigen (PSA) levels were retrospectively analysed for 887 men at presentation and on follow-up 1 year later. Following diagnosis, 150 men were managed conservatively and 586 men with drugs; 151 received surgery. **Results:** Overall median IPSS scores were 9.0 at baseline. Malay men most often had severe symptoms (17.3%), compared to other groups (Chinese 11.7%, Others 11.1%, Indians 10.7%). Indians most frequently showed improvement in the Quality of Life (QOL) score following intervention (64.3%). Malays had the poorest initial mean peak-flow rates (9.6 mL/s) and Chinese, the highest (12.0 mL/s). Initial post-void residual urine volume was highest in Malays (100.1 mL) but showed greatest reduction with medical treatment. Median IPSS scores decreased from 10.5 below 50 years old to 7.0 above 80 years old. Peak-flow rates were 12.6 to 7.2 mL/s respectively, with a corresponding upward trend in RU. Treatment with a combination of 5-alpha-reductase inhibitor and alpha-blocker yielded the greatest improvement in IPSS and QOL scores, and residual urine volume (71.4%, 60% and 68.8%, respectively). Indians had the lowest initial and follow-up PSA (1.5 and 1.2,  $P = 0.8$  and  $0.6$ , respectively). **Conclusions:** Inter-ethnic differences in symptom perception and quantitative assessment of BPH were evident among our multiracial urban study cohort, as well as varied degrees of response to the medical treatments instituted.

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**Key words:** International Prostate Symptom Score, Prostate specific antigen

### Introduction

Clinical observations suggest that BPH risk may vary by racial and ethnic group. However, data on the profile of prostatic symptoms in many Asian populations is lacking.<sup>1</sup> The majority of studies in current literature describe the ethnic variation within Western, and particularly white Caucasian populations, with only one community-based study performed in Singapore 10 years ago that compared a multiracial Singaporean study population with other international cohorts at the time.<sup>2</sup> Early clinical observations suggested that BPH risk varied by racial and ethnic group with black Afro-American men having the highest occurrence, followed by white Caucasian men, and then Asian men.<sup>3,4</sup> In more current studies, it has also been suggested that the incidence of benign prostate surgery

varied among ethnic groups, with Asian men possibly having lower surgery rates than their black or white counterparts. More detailed differentiation of inter-ethnic variation has been characterised within the Western white population as well, with studies describing differences among Welsh versus non-Welsh, and Jewish versus non-Jewish men, for example.<sup>5,6</sup>

Singapore has a relatively young immigrant population, and as such, study subjects would still have fairly distinct racial ethnic phenotypes and cultural backgrounds, while sharing largely similar urban living and working environments. Our retrospective case series sought to describe the baseline presentation of BPH in patients presenting to a tertiary hospital in Singapore as well as the subsequent progression of the disease with medical

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treatment, in particular focusing on the variations among ethnic and age groups in our multiracial Asian patient group.

### Materials and Methods

The records of 887 consecutive male patients diagnosed with BPH at our centre over a 2-year period between 2004 and 2006 were retrieved from the unit's BPH database. As standard protocol for all out-patient cases, once the clinical diagnosis was established, all such cases would be registered in the unit BPH database. The data set was maintained and updated by dedicated data entry staff, to ensure completeness of data. The patients were all referred from public primary healthcare polyclinics, private general practitioners or the hospital's emergency department, and were attended to by consultant-level staff of the Department of Urology in the hospital's Specialist Outpatient Clinic for complaints of lower urinary tract symptoms. In all cases, the diagnosis of BPH was made clinically at presentation, based on qualitative symptoms or quantitative assessment of bladder outlet obstruction. These were assessed using either the International Prostate Symptom Score (IPSS), or via measurement of uroflowmetry and post-void residual urine (RU) volume, respectively. Versions of the IPSS used in the study were validated translations in 1 of the 4 official national languages - English, Mandarin, Malay or Tamil - and were matched to the patients' native language or dialect as best possible. Based on their total composite IPSS score, patients were graded into subgroups with mild (total score of 1 to 7), moderate (total score of 8 to 19) and severe symptoms (total score of 20 or more). In addition, patients' response to the AUA Quality of Life (QOL) score and total prostate specific antigen (PSA) levels were also recorded. All of the above parameters were recorded at the time of presentation and on subsequent follow-up after 1 year, following either a conservative management approach, medical therapy or surgery. The choice of patient management was based on the severity of patients' obstruction at presentation, with transurethral resection of

the prostate (TURP) being offered to those with complications arising from the urinary obstruction, or with persistently low flow and severe symptoms despite maximal drug therapy.

Changes in patients' IPSS score, QOL score, uroflowmetry and RU volumes over the follow-up period were analysed by ethnic group and by age group. Patients who received medical therapy alone were stratified according to the drug received - Terazosin, Alfuzosin or Dutasteride with either of the former 2 alpha-adrenergic blockers - and their respective changes in the former 4 parameters were analysed. These changes were also recorded for patients who were treated with conservative management or surgery and reported for completeness of data, but comparison against these groups was not made in view of potential selection bias.

### Results

Of the 887 men studied, 677 were of Chinese ethnicity, 43 were Indian, 105 were Malay and 62 were from other ethnic minority groups. This distribution (76%, 5%, 12% and 7%, respectively) closely resembled the national population profile during the years covered by the database records, using national census figures from the 2005 National Household Survey for comparison (78%, 8%, 11% and 2%, respectively). Mean age of patients at presentation was 66 years; age distribution in the study group was normally distributed with the highest number of cases (31.2%) presenting at 60 to 69 years of age.

Overall median IPSS scores were 9.0 at baseline and likewise at the end of the observation period. Median initial IPSS were 9.0, 7.0, 10.0 and 12.0 for Chinese, Indian, Malay and other ethnic groups, respectively. Comparing by ethnic group, at presentation, Malay men were most commonly graded with severe symptoms (17.3%), followed by Chinese men (11.7%), other ethnic groups (11.1%) and then Indians (10.7%). Indian men were most commonly scored as having mild symptoms (53.6%), followed by Chinese (42.2%), other ethnic groups (37.8%) and then

Table 1. BPH Assessment Parameters for Major Ethnic Groups

	Chinese		Indian		Malay		Others	
	Initial	Follow-up	Initial	Follow-up	Initial	Follow-up	Initial	Follow-up
IPSS severity								
Severe (%)	11.7	8.6	10.7	11.9	17.3	13.3	11.1	0.0
Moderate (%)	46.1	53.6	35.7	35.2	55.8	50.0	51.1	52.0
Mild (%)	42.2	37.8	53.6	52.9	26.9	36.7	37.8	48.0
Qmax, mean (mL/s)	12.0	13.7	11.7	12.2	9.6	11.4	10.8	11.4
RU, mean (mL)	76.9	65.0	79.1	66.0	100.1	61.0	61.9	50.0

Qmax: uroflowmetry maximal flow rate; RU: residual urine volume

Malays (26.9%). A change from one IPSS severity classification to another by the end of the follow-up period was seen in near-equal proportion among the various ethnic groups (Table 1,  $P > 0.05$  for all 4 subgroups). Comparison of the patients' score on the AUA Quality of Life scale before and after intervention showed that Indians most frequently perceived an improvement in their score following intervention (64.3%) compared to other groups (Malays 50.0%, Others 41.7%, Chinese 40.9%) ( $P = 0.0004$ ). Comparing quantitative assessments, Malay men had poorest initial Qmax values of mean 9.6 mL/s but had the greatest improvement in Qmax at the end of the follow-up period with a mean increment of 1.8 mL/s ( $P = 0.87$ ); Indian men had the least eventual improvement in Qmax (11.7 to 12.2 mL/s). Initial post-void residual urine volume was highest in Malays (100.1 mL) but showed greatest reduction with medical treatment compared to

other ethnic groups, with a mean post-treatment difference of 39.1 mL ( $P = 0.19$ ).

Comparing by age group, overall severity of reported symptoms appeared to decrease with age. More mild symptoms and fewer moderate symptoms were reported with increasing age, with median reported IPSS scores decreasing from 10.5 to 7.0 from the youngest to oldest age band - contrasting with previously reported community data (Fig. 1). Uroflowmetry results showed an expected worsening trend with age, with median initial Qmax values decreasing from 12.6 to 7.2 mL/s for the  $<50$  and  $\geq 80$  years age groups, respectively, as well as a corresponding upward trend in RU with age (median 26 to 77 mL respectively, initial recorded RU).

Following diagnosis, 150 men were managed conservatively with watchful waiting and 586 men received only medical therapy. 151 received surgery during the 1 year course of their follow-up either at the outset or following a failed trial of drug therapy - 119 Chinese, 19 Malays, 8 Indians (18% respectively for each major ethnic

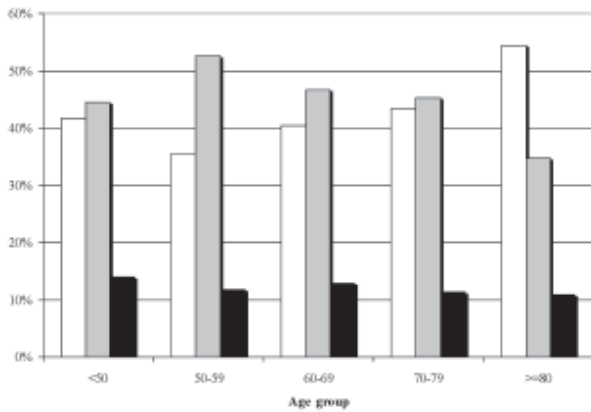


Fig. 1a.

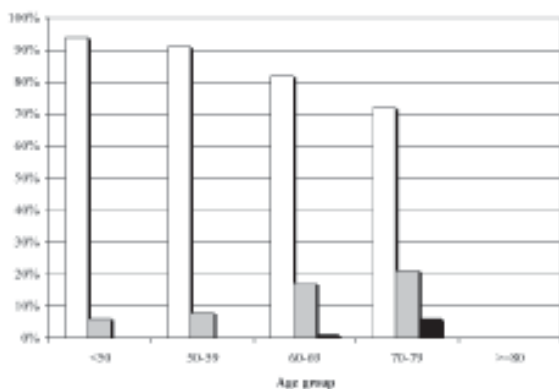


Fig. 1b.

□ Mild (IPSS 0 – 7)    ■ Moderate (IPSS 8 – 19)    ■ Severe (IPSS 20 – 35)

Fig. 1. Distribution of IPSS severity by age group in the study population (A) contrasting with results from a local community study (B); latter from: Tan HY, Choo WC, Archibald C, Esuvaranathan K. A community based study of prostatic symptoms in Singapore. J Urol 1997;157:890-3.

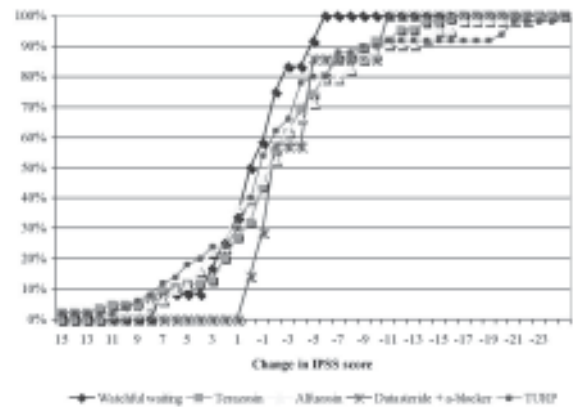


Fig. 2a.

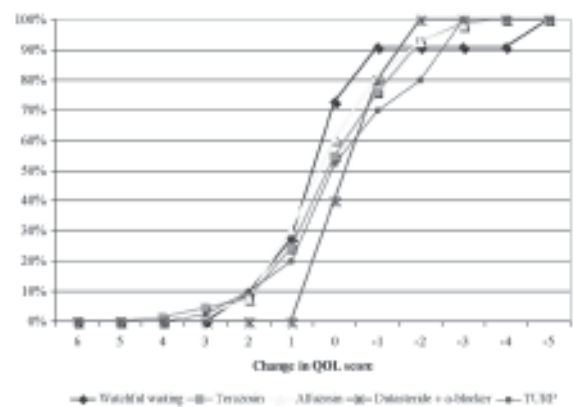


Fig. 2b.

Fig. 2. Cumulative incidence of change in IPSS and QOL scores according to drug treatment modality. Data points lying to the right of the chart indicate an improvement in symptoms. Data for cohorts treated conservatively and with surgery reflected for reference.

group), and 7 of other races. Of those who received only medical therapy, comparison of perceived response to treatment showed that the greatest improvement in IPSS and QOL scores were seen with the combination of 5-alpha-reductase inhibitor and alpha-blocker (71.4% and 60%, respectively; Figure 2). Conversely, patients who were managed conservatively perceived the least improvement in their IPSS and QOL scores (41.7% and 27.3%, respectively). Comparing the quantitative response to medical therapies, the single-agent Terazosin fared as well as combination therapy in improving Qmax (55.6% and 56.3%, respectively); marginally fewer patients demonstrated an improvement with Alfuzosin (53.0%) and watchful waiting (50.0%). Those receiving combination therapy showed the best improvement in RU volume (68.8%) compared to the Alfuzosin (50.8%) and Terazosin-only group (42.1%); of note, a similar percentage showed spontaneous improvement in serial RU without any treatment (45.8%).

Median initial PSA values were 2.1 ng/mL at presentation, showing a near-linear increase to 2.5 ng/mL at the end of the median 1-year follow-up. Indians had the lowest initial and follow-up PSA (1.5 and 1.2) compared to other ethnic groups ( $P = 0.8$  and  $0.6$ , respectively). Respective PSA values were higher and nearly equal in other ethnic groups - 2.6 and 2.3 in Chinese, 2.8 and 2.2 in Malays, and 2.5 and 2.0 in other ethnic groups. Univariate analysis did not show any correlation of PSA levels with the other qualitative or quantitative disease markers studied.

## Discussion

In this nationally and ethnically representative sample of men, we noted differences in the perception of lower urinary tract symptoms associated with BPH among the different major ethnic groups. Indian men tended to present with the mildest disease severity, recording the lowest initial IPSS scores and the highest initial Qmax values; whereas Malay men tended to present with more severe disease, with the highest initial IPSS and the poorest initial Qmax. This could represent differences in patient behaviour, with the former perhaps more willing to seek treatment, or more sensitive to perceived urinary symptoms. Of note, median initial IPSS for Indian men in our local migrant population (7.0) was lower than that recorded among those in the native community (12.2 [8.6]; mean [SD]).<sup>7</sup> Differences in native and migrant Chinese and Japanese populations have also been observed with regard to prostate volume, reinforcing the hypothesis of environmental and particularly diet-related factors on prostate growth and its corresponding symptoms.<sup>8</sup>

When compared with an earlier community-based study, we found paradoxical trends in IPSS scores reported among

men in the local community and those presenting to a tertiary centre such as ours. This finding could suggest treatment-avoidance behaviour, or under-reporting of symptoms particularly in our older patients, or a selection bias with fewer truly symptomatic older patients presenting to our hospitals for treatment. Notably, while similar Western community-based studies have been able to demonstrate an expected increasing prevalence of lower urinary tract symptoms and associated bother with age - albeit with inter-racial variation in prevalence of symptom types<sup>9-11</sup> - other data from the Southeast Asian region have likewise failed to show this correlation.<sup>12</sup> Despite the translated IPSS questionnaires having been validated in the 4 major languages used in this region, the accuracy of this instrument among older patients in the general community could be confounded by their preferential use of dialects, their overall lower literacy rate, or their difficulty in quantifying symptoms according to the set parameters of the IPSS. Furthermore, cultural differences may also account for the under-representation, with nocturia for example having been shown not to correlate consistently with perception of bother among our local ethnic groups<sup>7,13</sup> and Asian men having been known to be less likely to seek treatment for such symptoms.<sup>14</sup> As such, the translated IPSS questionnaires may have a lower than expected sensitivity as a measure of symptom severity, given these unique considerations among our local elderly patients. In addition, adaptive or compensatory behaviour or placebo effect after commencing medical drug therapy could further contribute towards some of the paradoxical observations noted in IPSS trends.

Quantitative response to treatment also varied by ethnic group, with Indians showing the least improvement in Qmax but best improvement in QOL score correspondingly at follow-up. While differences in Qmax between our studied ethnic groups have not been reported previously, differences in baseline uroflowmetry values among other races have been observed. Japanese men, for example, have been noted to have a higher baseline but a greater deterioration in Qmax with age when compared with American men, despite them having smaller prostate volumes.

Comparing medical treatment modalities, combination therapy with 5-alpha-reductase inhibitor and alpha-blocker yielded the greatest improvement in IPSS, QOL and RU parameters. This finding is consistent with current perspectives that combination therapy is the optimum non-surgical therapeutic option for long-term management of BPH,<sup>15,16</sup> and demonstrates its superiority in our local cohort even during a short 1 year treatment period. However, improvement in Qmax was not significant. Lepor et al also found weak correlation between changes in IPSS and

Qmax in all treatment groups, and suggested that Qmax may not be an accurate reflection of the degree of physiological bladder outlet obstruction. Despite the commonly assumed effect of 5-alpha-reductase inhibitors on reduction in prostate volume, Lepor also failed to show any significant relationship between changes in prostate volume and IPSS or Qmax.<sup>17</sup> Symptom reduction mediated by alpha-blockers' effect on prostatic smooth muscle relaxation may also be affected by non-smooth muscle alpha-1 receptors, which are associated with the sensory nervous system.

Even as presentation and response to treatment among Indians differed the most from the other ethnic groups in our cohort, we also found that Indian men had a distinctly lower PSA level than others, although not reaching statistical significance. Serum PSA levels have been noted to vary by ethnicity and geographical location, though not always amounting to a significant difference<sup>18-20</sup> nor correlating with related disease factors.<sup>21</sup> A community study showed that Singapore Chinese men had high mean PSA levels comparable to African-American men, with levels in both these groups higher than their White, Latino and Japanese-American counterparts, while at the same time, these higher levels among Singapore Chinese men did not correlate with their lower incidence of prostate cancer.<sup>22</sup> At present, similar data on PSA among Indian and Malay ethnic groups is lacking, but may provide further basis for inter-ethnic comparison when available.

The inter-ethnic differences observed have been postulated by some authors to reflect differences in factors influencing nodular epithelial prostatic growth such as the androgen signalling pathway, or those affecting prostatic smooth muscle tone.<sup>23,24</sup> Some have suggested that the ratio of prostatic stromal and epithelial cellular components and the area density of prostatic smooth muscle is related to symptom severity of BPH, and varies between racial groups. Prostates of Chinese men have been found to contain more glandular epithelial lumen and less smooth muscle and connective tissue than the prostates of White Caucasian-American men.<sup>25</sup> Differences in cellular composition have likewise been demonstrated in comparisons among African-Americans, Caucasian-Americans and Japanese.<sup>26</sup> Broader epidemiological studies such as the US Health Professionals Follow-up study noted that neither lifestyle factors such as diet and obesity, nor health factors such as blood pressure or heart rate was associated with the ethnic differences they noted among their White, Black and Asian study subgroups.<sup>27</sup> With more numbers and more detailed data collection, genetic and epigenetic factors unique to our Singaporean population could also be analysed for correlation and predictability of BPH severity and response to treatment in the light of histopathological findings, and

may provide further insight on the basis for our observations.

Our study was limited by its retrospective design and difficulties faced in administering the IPSS questionnaire, particularly to the dialect-speaking or non-literate elderly individuals who had trouble understanding even the validated translations of the questionnaire, and who unfortunately composed a fair proportion of the total study population. Furthermore, our study cohort was selected solely from a patient pool of a tertiary hospital, and as such may be subject to selection bias. A broader-based study including patients treated by both hospital-level specialists, as well as general practitioners at primary healthcare facilities may correct for this confounder, and may provide a fairer comparison of response to drug treatments that are accessible at both levels.

## Conclusion

Inter-ethnic differences in symptom perception and quantitative assessment of BPH presentation and progression were evident among our multiracial urban Asian study cohort. Response to treatment among Indian men differed the most from other ethnic groups, corresponding with a consistently lower PSA level than the rest. Compared with community-based study data, paradoxical trends in IPSS scores in our study may suggest limitations in the use of the translated questionnaire as an accurate measurement tool for BPH symptom severity particularly among our elderly patients. Our local data also supported current evidence that combination therapy with 5-alpha-reductase inhibitor and alpha-blocker was the best regimen for non-surgical management of BPH symptoms.

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