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ORIGINAL ARTICLE

Prostate Disease

Age-related changes for the predictors of benign prostatic hyperplasia in Chinese men aged 40 years or older

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A cross-sectional study was conducted to estimate the age-stratified normal levels and age-related changes in the risk predictors of benign prostatic hyperplasia (BPH) progression. A total of 4706 male participants aged 40 years or older in Zhengzhou (China) were enrolled. The values of the International Prostate Symptom Score (IPSS), prostate-specific antigen (PSA), prostate volume (PV), and postvoid residual urine volume (PVR) significantly increased with age. Nonlinear relationships between age and IPSS scores ≥8 (*P* for nonlinearity = 0.046), PSA level ≥1.6 ng ml^{-1}, PV ≥31 ml, or PVR ≥39 ml (all *P* for nonlinearity <0.001) were observed. After the age of 61 years, the risk indicators related to BPH progression were positively correlated with age (odds ratio [OR] >1), regardless of the predictors of the IPSS score, PSA level, PV, or PVR; and the OR values increased gradually. Therefore, after the age of 61 years, the risk predictors related to BPH progression were positively correlated with age.

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Keywords: aging; lower urinary tract symptoms; postvoid residual urine volume; prostate-specific antigen; prostate volume

INTRODUCTION

Benign prostatic hyperplasia (BPH), a chronic and progressive disease, is one of the most common diseases among aging men.[1,2] In China, the estimated prevalence of BPH is 36.6%, and it increases markedly from 2.9% in men aged 40–49 years to 69.2% in men aged 80 years or older.[3] Although BPH is not life threatening, it is associated with an increased risk of cardiovascular diseases and is related to sleep, mental health, sexual function, and a series of disorders.[4–6] In addition, medical and surgical treatments for BPH and incidental complications also add to the cost burden.[7,8]

The diagnosis of BPH is based on thorough examinations, including assessments of lower urinary tract symptoms (LUTS), digital rectal examinations (DREs), urinalysis, prostate-specific antigen (PSA) levels, transrectal ultrasounds, postvoid residual urine volume (PVR), and urodynamics.[9,10] Studies have shown an increased risk of BPH progression with worse LUTS, a larger prostate volume (PV), a higher PSA level, an increased PVR, and a decreased maximum urinary flow rate (Q_{max}),[11–13] which were defined as risk predictors of BPH progression if their values reached the threshold.[14] Furthermore, these predictors changed with age.[15,16] However, few studies have estimated normal levels of these predictors by age groups based on large-scale populations, especially for healthy individuals in Asia.

We conducted this cross-sectional study in Zhengzhou (China) to estimate age-stratified normal levels and age-related changes in the risk predictors of BPH progression, which may provide evidence for the clinical diagnosis and management of BPH.

PARTICIPANTS AND METHODS

Study population

Data were obtained from the Prostate Cancer Screening Program in Zhengzhou, China. The multistage stratified random sampling method was conducted to recruit participants. Fifteen communities or villages from seven districts or towns were randomly selected in Zhengzhou. Healthy male residents in Zhengzhou aged 40 years or older were invited to volunteer for the program. A total of 6282 men participated in the study from October 2019 to March 2021. Informed consent was obtained from all individual participants included in the study. The study was approved by the Grass-roots Ethics Review Committee of The Third People's Hospital of Zhengzhou (Zhengzhou, China; No. 2019-04-006-K01).

All investigations were based on community health service centers. Eligible participants completed a face-to-face survey based on a baseline questionnaire. The following general information was obtained: age, place of residence (rural or urban), self-reported disease history (including hypertension, hyperlipidemia, diabetes, BPH, prostate cancer, and other urinary diseases), surgical treatment, and medication use for prostate diseases. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared (kg m^{-2}). BMI was divided into four

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groups: underweight (<18.5 kg m^{-2}), normal weight (≥18.5 kg m^{-2} and <25.0 kg m^{-2}), overweight (≥25.0 kg m^{-2} and <30.0 kg m^{-2}), and obese (≥30.0 kg m^{-2}).

LUTS were estimated by the 8-item International Prostate Symptom Score (IPSS) questionnaire, which includes items on urinary frequency, urgency, intermittency, straining, weak stream, incomplete bladder emptying, nocturia frequency, and quality of life (QoL) scores.[17] Higher scores indicate more severe symptoms. Nocturia was defined as getting up to urinate two or more times during the night.[6] Furthermore, the participants provided blood samples for PSA tests and received physical examinations and DREs. PVR and PV were measured by abdominal ultrasound examinations. PVR was calculated as 0.52 times the height, width, and length of the empty bladder: PVR = 0.52 × (height × width × length); PV was calculated as π/6 times the width, height, and length of the prostate: PV = π × (height × width × length)/6. Individuals included in this analysis met the following criteria: men aged 40 years or older and those with DREs and ultrasound examinations that proved no abnormal nodules or enlargement of the prostate. The exclusion criteria were as follows: men with a history of BPH, prostate cancer, bladder cancer, urinary tract infection, urolithiasis, or other severe illness; men who received surgical treatments or used medications, including alpha-adrenergic antagonists (alpha-blockers) and 5-alpha-reductase inhibitors (5-ARIs) for prostate diseases; and men with missing data. In the present study, a total sample of 4706 individuals were included.

We defined the risk predictors of clinical progression of BPH as IPSS score ≥8, PSA level ≥1.6 ng ml^{-1}, PV ≥31 ml, or PVR ≥39 ml.[14]

Statistical analyses

Men were categorized into the following seven age groups: 40–44 years, 45–49 years, 50–54 years, 55–59 years, 60–64 years, 65–69 years, 70–74 years, and ≥75 years. The number and percentage of each age group are presented in **Table 1**. Mean with standard deviation (s.d.) was computed for PV, IPSS score, PSA level, and PVR by age groups. Wilcoxon rank-sum tests were used for comparisons. Moreover, 95% confidence interval (95% CI) was used to estimate reference ranges among the different age groups. In addition, we explored potential nonlinear associations between age and the predictors of the risk of clinical progression of BPH using logistic regression models with restricted cubic spline analyses. The analyses were adjusted for marital status, education level, place of residence, BMI, smoking status, drinking status, and history of hypertension, hyperlipidemia, and diabetes. A two-tailed $P < 0.05$ for the two sides was considered statistically significant. All analyses were performed with R version 4.1.0 (Lucent Technologies, Vienna, Austria). The data that support the findings of this study are available upon request from the corresponding author (WDZ). The data are not publicly available because of privacy or ethical restrictions.

Table 1: Demographic data and clinical characteristics of the participants (total *n*=4706)

Characteristic	*Participants, n (%)*	*IPSS score*		*QoL*		*PSA level (ng ml^{-1})*		*PV (ml)*		*PVR (ml)*	
		Mean±s.d.	*P*	*Mean±s.d.*	*P*	*Mean±s.d.*	*P*	*Mean±s.d.*	*P*	*Mean±s.d.*	*P*
Age group (year)			<0.001		<0.001		<0.001		<0.001		<0.001
40–44	238 (5.1)	2.72±3.49		1.95±1.20		1.73±1.03		18.20±7.63		1.74±4.97	
45–49	447 (9.5)	3.30±3.99		2.13±1.18		1.80±1.04		20.36±7.43		3.38±15.86	
50–54	692 (14.7)	3.50±3.80		2.25±1.14		1.90±1.15		21.82±9.22		3.16±7.48	
55–59	813 (17.3)	4.60±5.01		2.34±1.19		2.08±2.11		23.30±9.81		3.56±9.54	
60–64	811 (17.2)	5.49±5.47		2.47±1.17		2.20±1.57		23.75±10.29		6.08±18.80	
65–69	928 (19.7)	5.71±5.58		2.49±1.18		2.46±2.66		25.76±12.01		5.57±13.63	
70–74	524 (11.1)	7.51±6.59		2.69±1.15		2.76±4.07		25.47±11.49		7.85±16.59	
≥75	253 (5.4)	8.15±6.58		2.71±1.16		3.26±6.72		29.88±24.49		8.57±17.41	
BMI group (kg m^{-2})			0.482		0.449		0.022		0.336		0.192
Underweight (<18.5)	41 (0.9)	5.80±6.94		2.27±1.32		1.92±0.93		21.93±9.02		10.17±43.72	
Normal (≥18.5 and <25.0)	1912 (40.6)	5.09±5.50		2.38±1.20		2.29±2.35		23.40±11.96		4.95±14.71	
Overweight (≥25.0 and <30.0)	2288 (48.6)	5.02±5.25		2.40±1.17		2.24±3.23		23.94±11.78		5.04±13.00	
Obese (≥30.0)	465 (9.9)	5.55±5.64		2.46±1.20		2.09±1.41		23.97±10.48		4.25±10.17	
Residence			0.043		0.079		<0.001		<0.001		<0.001
Rural	2701 (57.4)	5.17±5.69		2.37±1.21		2.37±2.82		22.39±10.27		4.29±14.13	
Urban	2005 (42.6)	5.03±5.01		2.44±1.15		2.07±2.61		25.47±13.20		5.89±13.84	
Hypertension			<0.001		<0.001		0.073		0.005		0.029
Yes	1618 (34.4)	5.84±5.71		2.51±1.21		2.34±3.39		24.11±10.79		6.09±17.52	
No	3088 (65.6)	4.72±5.21		2.34±1.17		2.19±2.32		23.49±12.16		4.38±11.75	
Hyperlipidemia			<0.001		<0.001		0.008		0.108		0.023
Yes	618 (13.1)	6.14±5.74		2.66±1.14		2.14±2.75		24.08±11.11		6.30±15.87	
No	4088 (86.9)	4.95±5.34		2.36±1.19		2.26±2.74		23.65±11.80		4.77±13.72	
Diabetes			<0.001		<0.001		0.004		0.561		0.001
Yes	575 (12.2)	6.24±5.50		2.60±1.14		2.07±1.80		23.75±10.18		8.39±23.13	
No	4131 (87.8)	4.95±5.38		2.37±1.19		2.27±2.84		23.70±11.91		4.49±12.16	
Nocturia			<0.001		<0.001		0.638		<0.001		<0.001
Yes	2250 (47.8)	7.76±5.93		2.02±1.14		2.35±3.46		24.21±12.41		6.52±17.31	
No	2456 (52.2)	2.67±3.39		2.81±1.09		2.14±1.84		23.24±11.01		3.54±9.92	

Wilcoxon rank-sum tests were used for comparisons. IPSS: International Prostate Symptom Score; s.d.: standard deviation; QoL: quality of life; PSA: prostate-specific antigen; PV: prostate volume; BMI: body mass index; PVR: postvoid residual urine volume

RESULTS

A total of 4706 men were enrolled in the analysis, and the age (mean ± s.d.) was 60 ± 9 years. The BPH-related factors according to characteristics are presented in **Table 1**. A total of 83.5% of the participants were under 70 years old. For the mean comparisons, there were significant differences in IPSS score, PSA level, PV, and PVR among age groups (all $P < 0.001$). We found that rural residents had higher IPSS score and PSA level and smaller PV and PVR. In addition, higher values of IPSS score, QoL, and PVR were observed among males with a history of hypertension, hyperlipidemia, diabetes, or nocturia. Men with a history of hypertension and nocturia had larger PV and men with a history of hyperlipidemia had lower PSA level.

The mean value with 95% CI for IPSS score, PSA level, PV, and PVR is presented in **Table 2** and **Figure 1**. For IPSS score (**Table 2** and **Figure 1a**), the mean score value was 5.11 (95% CI: 4.95–5.26), and it increased from 2.72 (95% CI: 2.28–3.17) for men aged 40–44 years to 8.15 (95% CI: 7.34–8.97) for those aged 75 years and older. Similarly, the values of PSA, PV, and PVR significantly increased with age (**Table 2** and **Figure 1b**–**1d**), especially for individuals aged under 70 years.

Logistic regression models with restricted cubic spline analyses were used to explore the nonlinear associations after controlling for potential confounders (**Figure 2**). A J-shaped dose–response relationship between age and IPSS score ≥8 (P for nonlinearity = 0.046; **Figure 2a**) was observed. In addition, there were S-shaped dose–response relationships between age and PSA level ≥1.6 ng ml^{-1}, PV ≥31 ml, and PVR ≥ 39 ml (all P for nonlinearity <0.001; **Figure 2b**–**2d**). As **Figure 2a** shows, age was positively correlated with IPSS score ≥8 after 61 years of age (odds ratio [OR] >1), and OR values increased gradually with age. Likewise, age was positively associated with PSA level ≥1.6 ng ml^{-1}, PV ≥31 ml, or PVR ≥39 ml. The OR values increased rapidly after the age of 61 years and remained stable after the age of 70 years (**Figure 2b** and **2c**). Therefore, the risk predictors of BPH progression were positively correlated with age after 61 years, regardless of the predictors of the IPSS score, PSA level, PV, or PVR.

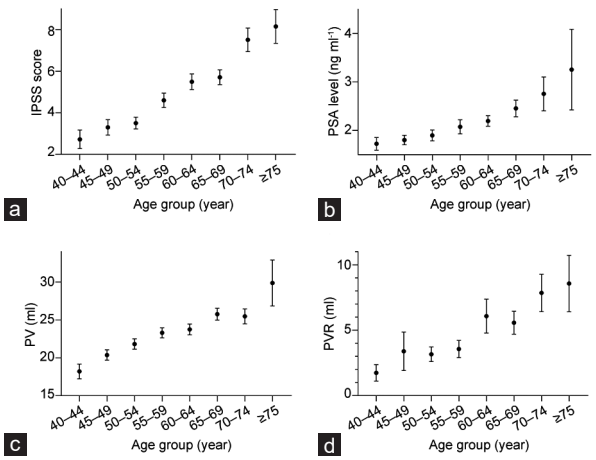

Figure 1: Mean value and 95% CI by age group for (**a**) IPSS score, (**b**) PSA level, (**c**) PV, and (**d**) PVR. CI: confidence interval; IPSS: International Prostate Symptom Score; PSA: prostate-specific antigen level; PV: prostate volume; PVR: postvoid residual urine volume.

DISCUSSION

BPH usually develops after 40 years of age, and the present study included men aged 40 years or older in Zhengzhou. We estimated age-stratified characteristics and age-related changes in BPH progression-related predictors, including the IPSS score, PSA level, PV, and PVR. The results showed that the values of the IPSS score, PSA, PV, and PVR significantly increased with age. Meanwhile, the risk predictors of BPH progression were positively correlated with age after 61 years.

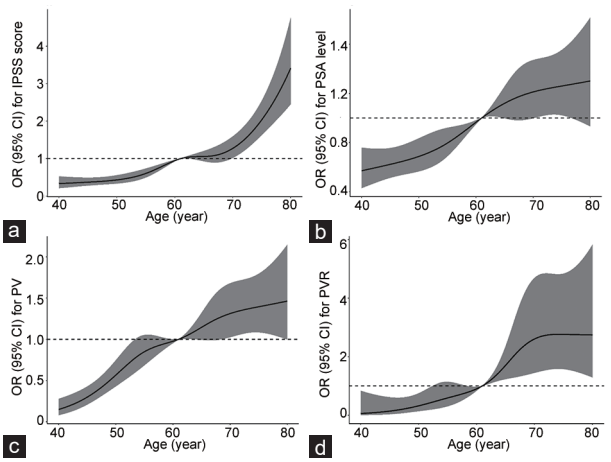

Figure 2: Associations among age and (**a**) IPSS score ≥8, (**b**) PSA level ≥1.6 ng ml^{-1}, (**c**) PV ≥31 ml, and (**d**) PVR ≥39 ml. Logistic regression models with restricted cubic spline analyses adjusted for marital status, education level, residence, BMI, smoking status, drinking status, and history of hypertension, hyperlipidemia, and diabetes. IPSS: International Prostate Symptom Score; PSA: prostate-specific antigen; PV: prostate volume; PVR: postvoid residual urine volume; OR: odds ratio; CI: confidence interval; BMI: body mass index.

Table 2: Mean values and 95% CIs of patient characteristics by age group

Age group (year)	*IPSS score*		*Total PSA level (ng ml^{-1})*		*PV (ml)*		*PVR (ml)*	
	Mean	*95% CI*	*Mean*	*95% CI*	*Mean*	*95% CI*	*Mean*	*95% CI*
40–44	2.72	2.28–3.17	1.73	1.59–1.86	18.20	17.23–19.18	1.74	1.11–2.37
45–49	3.30	2.92–3.67	1.80	1.71–1.90	20.36	19.67–21.06	3.38	1.91–4.86
50–54	3.50	3.22–3.79	1.90	1.79–2.01	21.82	21.13–22.51	3.16	2.60–3.72
55–59	4.60	4.25–4.94	2.08	1.93–2.22	23.30	22.63–23.98	3.56	2.91–4.22
60–64	5.49	5.11–5.87	2.20	2.09–2.31	23.75	23.04–24.46	6.08	4.78–7.37
65–69	5.71	5.35–6.07	2.46	2.28–2.63	25.76	24.98–26.53	5.57	4.69–6.45
70–74	7.51	6.95–8.08	2.76	2.41–3.11	25.47	24.48–26.45	7.85	6.43–9.27
≥75	8.15	7.34–8.97	3.26	2.42–4.09	29.88	26.84–32.91	8.57	6.41–10.72
Total	5.11	4.95–5.26	2.24	2.16–2.32	23.70	23.37–24.04	4.97	4.57–5.37

IPSS: International Prostate Symptom Score; PSA: prostate-specific antigen; PV: prostate volume; PVR: postvoid residual urine volume; CI: confidence interval

Consistent with previous studies, BPH-related indicators were positively correlated with age.[15,18] The age-stratified levels of PV in the present study were comparable to those estimated in Germany[15] but lower than those estimated in America,[19] The Netherlands,[20] and Korea[18] and higher than those in Japan[21] and a rural area in China[22]. Moreover, the age-specific values of PSA were comparable to those in Japan[21] but higher than those in Germany.[15] The scores of IPSS by age groups were similar to the results in Germany, while the values of PVR by age group were lower than those in Germany.[15] However, the included participants and study designs of these studies were varied, so it is necessary to compare these predictors among different races.

We explored nonlinear associations between age and the risk predictors of BPH progression. The J-shaped or S-shaped dose–response relationships showed an increased risk of BPH progression with age, especially for men aged 61 years or older. Although the mechanisms of BPH development and progression with increased age are unclear, BPH has been proposed to be associated with metabolic derangements, impaired hormone balance, and chronic inflammation.[9] Age-related cardiovascular risk factors, such as central obesity, insulin resistance, and hypertriglyceridemia, are attributed to an increased risk of BPH.[23] The mechanisms may be that damage of the atherosclerotic vasculature on the pelvic vasculature supplying the bladder and prostate may contribute to prostate epithelial hyperplasia and cause the overactivity of neuroendocrine systems.[24,25] Studies also revealed that androgen changes with age played an important role in the etiology of BPH.[26] In addition, chronic inflammation may promote the growth of prostate cells and aggravate the severity of LUTS.[27,28]

We conducted this cross-sectional study based on the community population. There were also some limitations in this study. First, this analysis was a secondary analysis based on the screening program, and urodynamic tests were not measured. Urodynamic measurements can help to determine the presence of bladder obstructions, and a Q_{max} less than 10.6 ml s^{-1} was suggestive of a risk of BPH progression.[9,14] Second, the participants' disease histories were self-reported, and other disorders may have influenced the results. Third, the present study was a cross-sectional study, and we could not estimate the longitudinal changes and change rates of these predictors.

CONCLUSIONS

Age-stratified normal values of BPH progression-related predictors, including the IPSS score, PSA level, PV, and PVR, were estimated among men aged 40 years or older in China. The results showed that the risk factors related to BPH progression were positively correlated with age after the age of 61 years.

AUTHOR CONTRIBUTIONS

WHS and CFZ contributed completely to the writing of this paper. WDZ, YCG, and CFC were involved in the study concept and design. XRC and BWZ acquired and collated the data in this study. WHS, CFZ, and GLW carried out data analysis and interpretation. WDZ supervised the study. All authors read and approved the final manuscript.

COMPETING INTERESTS

All authors declare no competing interests.

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