Low Serum Testosterone But Not Obesity Predicts High Gleason Score at Biopsy Diagnosed as Prostate Cancer in Patients with Serum PSA Lower than 20 ng/ml

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Abstract. *Background/Aim: The impact of testosterone or obesity on the pathological grade of prostate cancer remains controversial. Therefore, in this study, we investigated the relationship of serum testosterone and body mass index (BMI) to Gleason score at biopsy. Patients and Methods: This study included 128 Japanese patients diagnosed with prostate cancer from 2000 through 2012 whose serum testosterone level and BMI were measured before treatment. Associations between clinical parameters, including pre-treatment serum testosterone level and BMI, and Gleason score at biopsy were examined. Results: The median serum testosterone and BMI were 434 ng/dl (interquartile range=362-542 ng/dl) and 23.5 kg/m^2 (interquartile range=21.7-25.4 kg/m^2), respectively. Gleason score at biopsy was <7, 7 and >7 for 58 patients (45.3%), 52 patients (40.6%) and 18 patients (14.1%), respectively. On univariate analysis, positive finding at digital rectal examination (DRE), high prostate-specific antigen level at diagnosis and low serum testosterone level, but not BMI, were correlated with high Gleason score at biopsy. Multivariate analysis identified positive finding at DRE and low serum testosterone level as significant predictors of a high Gleason score at prostate biopsy. By combining these parameters, the predictive ability of a high Gleason score was improved. Conclusion: This study showed that positive finding at DRE and a low pre-treatment serum testosterone level, but not obesity, may be factors predictive of aggressive prostate cancer, indicating the diagnostic value of serum testosterone, as well as DRE findings, in risk assessment.*

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Since the introduction of prostate-specific antigen (PSA) screening, the prevalence of prostate cancer has dramatically increased and patients are now diagnosed at an earlier stage in the United States, as well as in other developed countries, including Japan. Accordingly, prostate cancer has become one of the most common types of cancer among men in developed countries (1). However, over-diagnosis and over-treatment of low-risk prostate cancer have become subjects of debate. Therefore, precise risk assessment of prostate cancer is critical in prostate cancer diagnosis and therapeutics. Advanced age, race such as African American, positive findings at digital rectal examination (DRE), and high serum PSA level are well-known predictors of a high Gleason score (2), which is the gold standard pathological classification indicating malignant potential in prostate cancer, and one of the critical determinants in risk classification, in addition to serum PSA level at diagnosis and clinical T-stage.

Previous studies have shown that androgens are possibly associated with prostate cancer incidence (3) as well as pathological grade (4-6). In contrast, some studies failed to show any significant association between serum testosterone and prostate cancer incidence or pathological grade (3). However, obesity, represented by body mass index (BMI), has also been associated with prostate cancer incidence (7) and aggressive prostate cancer (8, 9). Consistent with this finding, one study showed that obese men in the United States with a BMI higher than 30 kg/m^2 that underwent radical prostatectomy (RP) presented disease with a high Gleason score (10). In contrast, other studies failed to show significant association between obesity and Gleason score at RP in European (11) and Japanese cohorts (12).

These studies suggest that testosterone and obesity represented by BMI are possible predictors of Gleason score in prostate cancer. In addition, the serum testosterone level has been reported to be inversely correlated with BMI among men (13). However, the association between both these parameters and Gleason score remains controversial, and comprehensive

analysis using both parameters is limited. Therefore, in order to establish their significance in diagnosis of prostate cancer, we examined the impact of serum testosterone and BMI on Gleason score, as well as the correlation between serum testosterone and BMI among men with prostate cancer with a serum PSA level of less than 20 ng/ml level at diagnosis.

Patients and Methods

This study enrolled Japanese patients with prostate cancer whose serum testosterone level and BMI were measured before treatment and who were treated at the Kyushu University Hospital (Fukuoka, Japan) from 2000 to 2012. Blood from patients was taken between 8:00 and 10:00 in the morning and serum testosterone was measured by electrochemiluminescence immunoassay method. This study was approved by the Institutional Review Board (approval number 26-2). All patients were histopathologically diagnosed with adenocarcinoma of the prostate. Patients that underwent androgen-deprivation therapy (ADT) before biopsy were excluded. To highlight diagnostic relevance, patients with a PSA level over 20 ng/ml diagnosed with prostate cancer were excluded. Accordingly, 128 patients were identified and then analyzed. Among the 128 patients, 50 men were biopsied at Kyushu University Hospital by ultrasound-guided transperineal sextant 12-core biopsy, while the remaining 78 men were biopsied at referral institutions and the biopsy specimens from 41 cases were reviewed at our institution. After 2006, at our institution, Gleason scores in 39 patients were evaluated according to the modification at the 2005 International Society of Urological Pathology Consensus Conference (14). Clinical T-stage was determined in accordance with the unified TNM criteria based on the results of DRE, transrectal ultrasound and magnetic resonance imaging (15). With regard to treatment, 34, 76, and 18 men were treated with RP, radiotherapy, and ADT, respectively. Among the 34 patients that underwent RP, six were treated with neoadjuvant ADT.

All statistical analyses were performed using JMP9 software (SAS Institute, Cary, NC, USA). The correlations between parameters were examined by Student's *t*-test, Pearson's test and Pearson product–moment correlation coefficient. Univariate and multivariate analyses were performed using the logistic regression model. *p*-Values of less than 0.05 were considered significant.

Results

The clinical and pathological characteristics of the 128 Japanese patients enrolled in this study are shown in Table I. The median age of the patients was 71 years [interquartile range (IQR)=64-75 years) and the median serum PSA level was 8.7 ng/ml (IQR=6.6-12.0 ng/ml) at diagnosis. Among the 128 patients, disease in 70 (54.7%), 36 (28.1%) and 16 (12.5%) patients was diagnosed as cT1, cT2 and cT3, respectively. A total of 47 (36.7%) men had palpable disease by DRE. Median serum testosterone and BMI were 434 ng/dl (IQR=362-542 ng/dl) and 23.5 kg/m^2 (IQR=21.7-25.4 kg/m^2), respectively.

The Gleason scores of biopsy specimens were <7, 7 and >7 for 58 patients (45.3%), 52 patients (40.6%) and 18 patients (14.1%), respectively (Table II). Among men that had undergone RP without neoadjuvant ADT, the majority of patients (57.1%) had a Gleason score at RP that was concordant with Gleason score at biopsy (Table III). Using this cohort, we performed univariate and multivariate analyses for the associations between clinical parameters, including age, DRE findings, serum PSA at diagnosis, serum testosterone level, BMI and Gleason score of biopsy specimens. On univariate analysis, positive DRE finding, high serum PSA level and low serum testosterone level as continuous variables, but not BMI, were significant predictors of high Gleason score at biopsy (Table II). As shown in Figure 1, patients were divided according to Gleason score using these variables. When tumor was palpable by DRE, the proportion of patients with a high Gleason score increased (Figure 1A, $p<0.0001$). With regard to PSA level, the proportion of those with a high Gleason score increased with increasing serum PSA (Figure 1B; left, $p=0.050$; right, $p=0.0070$). In contrast, the proportion of those with a high Gleason score increased with decreasing serum testosterone level (Figure 1C; left, $p=0.083$; right, $p=0.042$). However, because these parameters may be confounding factors, we performed multivariate analysis on these factors. On multivariate analysis, only positive DRE finding and a high serum testosterone level as continuous variables were significant predictors of a high Gleason score at biopsy (Table II).

Table I. *Patients' characteristics*.

Variable (n=128)	
Madian age (IQR), years	71 (64-75)
DRE, n (%)	
Palpable	47 (36.7%)
Non-palpable	81 (63.3%)
Clinical stage, n (%)	
cT1	70 (54.7%)
cT2	36 (28.1%)
cT3	16 (12.5%)
NA	6
Median PSA at diagnosis (IQR), ng/ml	8.7 (6.6-12.0)
Q1	3.1-6.5
Q2	6.6-8.6
Q3	8.7-11.9
Q4	12.0-19.7
Median testosterone at diagnosis (IQR), ng/dl	434 (362-542)
Q1	41-362
Q2	363-433
Q3	434-540
Q4	541-845
Median BMI at diagnosis (IQR), kg/m^2	23.5 (21.7-25.4)
Q1	16.0-21.7
Q2	21.8-23.3
Q3	23.4-25.3
Q4	25.4-31.6

IQR, Interquartile range; NA, not available; DRE, digital rectal examination; PSA, prostate-specific antigen; BMI, body mass index.

Table II. *Association between clinical parameters and Gleason score at biopsy*

Variable	Gleason score			Univariate	Multivariate
	<7 (n=58, 45.3%)	7 (n=52, 40.6%)	>7 (n=18, 14.1%)	*p*-Value	*p*-Value
Median age (IQR), years	70 (64-74)	69 (63-75)	74 (69-78)	0.070	
DRE, n (%)					
Palpable	13 (22.4%)	18 (34.6%)	16 (88.9%)		
Non-palpable	45 (77.6%)	34 (65.4%)	2 (11.1%)	<0.0001*	0.0001*
Median PSA at diagnosis (IQR), ng/ml	8.2 (6.2-11.3)	8.6 (6.6-11.8)	11.5 (9.1-15.4)	0.0070*	0.1
Q1, n (%)	19 (32.8%)	13 (25.0%)	0 (0.0%)		
Q2, n (%)	14 (24.1%)	15 (28.8%)	3 (16.7%)		
Q3, n (%)	13 (22.4%)	13 (25.0%)	6 (33.3%)		
Q4, n (%)	12 (20.7%)	11 (21.2%)	9 (50.0%)	0.050*	
Median testosterone at diagnosis (IQR), ng/dl	444 (377-556)	463 (370-554)	350 (272-402)	0.0042*	0.0012*
Q1, n (%)	11 (19.0%)	12 (23.1%)	9 (50.0%)		
Q2, n (%)	14 (25.9%)	11 (21.2%)	6 (33.3%)		
Q3, n (%)	14 (25.9%)	15 (28.8%)	2 (11.1%)		
Q4, n (%)	17 (29.3%)	14 (26.9%)	1 (5.6%)	0.083	
Median BMI at diagnosis (IQR), kg/m2	23.5 (21.9-25.7)	23.4 (21.6-25.2)	23.3 (21.1-24.9)	0.81	
Q1, n (%)	13 (22.4%)	13 (25.0%)	6 (33.3%)		
Q2, n (%)	16 (27.6%)	12 (23.1%)	4 (22.2%)		
Q3, n (%)	12 (20.7%)	15 (28.8%)	5 (27.8%)		
Q4, n (%)	17 (29.3%)	12 (23.1%)	3 (16.7%)	0.84	

IQR, Interquartile range; DRE, digital rectal examination; NA, not available; PSA, prostate-specific antigen; RRP, retropubic radical prostatectomy; LRP, laparoscopic radical prostatectomy; RALP, robot-assisted laparoscopic radical prostatectomy.

Next, the diagnostic value of DRE findings and serum testosterone level was evaluated by receiver operator characteristic (ROC) curve. As shown in Figure 2A, the DRE finding was valuable in diagnosis of high Gleason score (>7) prostate cancer [area under the curve (AUC)=0.80, sensitivity=0.89, specificity=0.72]. Similarly, the serum testosterone level was valuable for diagnosis, especially of prostate cancer with Gleason score higher than 7 (AUC=0.76, sensitivity=0.78, specificity=0.67) (Figure 2B).

Subsequently, combining these two significant predictors of a high Gleason score (DRE finding and serum testosterone level), a predictive model was created. Positive DRE finding and a serum testosterone level lower than the median (<434 ng/dl) were scored as 1, and the sum of the two scores was used as a variable. As shown in Figure 3A, the proportion of patients with a high Gleason score increased with increasing sum score of DRE finding and serum testosterone level ($p<0.0001$). By combining these parameters, the predictive ability for a high Gleason score (>7) was improved (AUC=0.86, sensitivity=0.72, specificity=0.89) (Figure 3B).

However, there was no correlation between serum testosterone level and serum PSA level or DRE findings (Table IV). In addition, there was no correlation between serum testosterone level and age or BMI in this cohort (Table IV, Figure 4), although serum testosterone level has been reported to be associated with age and BMI in healthy men (16).

Discussion

Previous reports showed that age, race, DRE finding, and serum PSA level at diagnosis were strong predictors of tumor aggressiveness represented by Gleason score (2). Additionally, several clinicopathological parameters, including serum testosterone level and obesity (BMI) were suggested to be associated with Gleason score. Furthermore, a low serum level of male hormone was shown to be associated with a high Gleason score (4-6, 17, 18). In line with these findings, this study showed the significance of serum testosterone in predicting Gleason score at biopsy. However, several studies failed to show a significant relationship between serum male hormone level and Gleason score, or conversely showed increased Gleason score in men with a higher serum testosterone level (3). Because serum testosterone levels may differ among ethnic groups (19, 20), ethnic difference in or among cohorts may account for the controversial results in studies on the relationship between serum male hormone level and Gleason score. Additionally, different conditions among studies might also contribute to the controversial results.

Several hypotheses on the relationship between serum testosterone and prostate cancer characteristics, such as the classical linear model, as well as a U-shaped model (21) and a saturation model (22, 23) as non-linear models, have been proposed. The findings in this study support the saturation model rather than the U-shaped model, as indicated in Figure 1C.

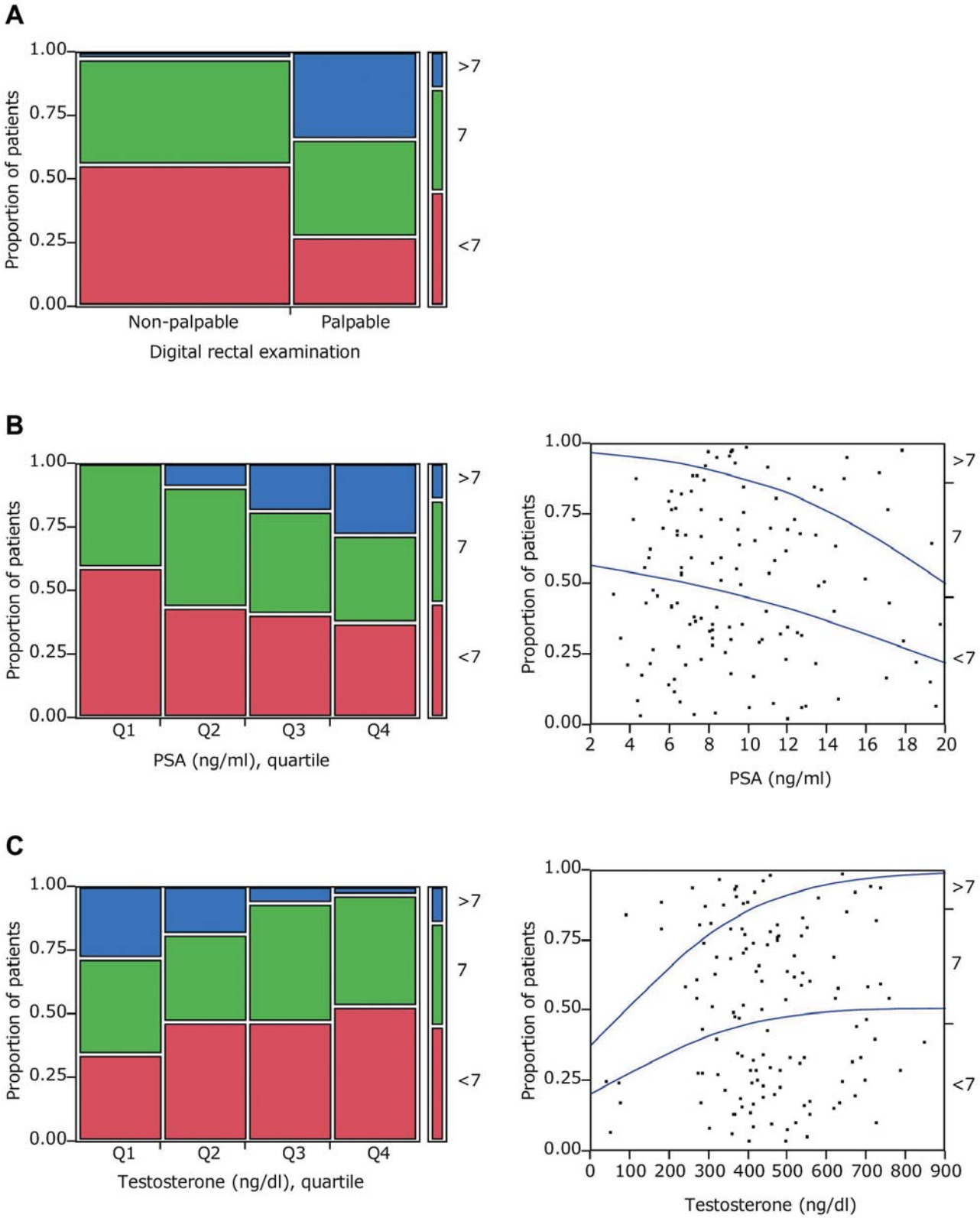

Figure 1. *Associations between clinical parameters and Gleason score at biopsy. The associations between digital rectal examination finding (A), prostate-specific antigen (PSA) level (B), serum testosterone level (C) and Gleason score at biopsy are shown. Left and right panels in (B) and (C) indicate categorized (quartile) and continuous variables, respectively.*

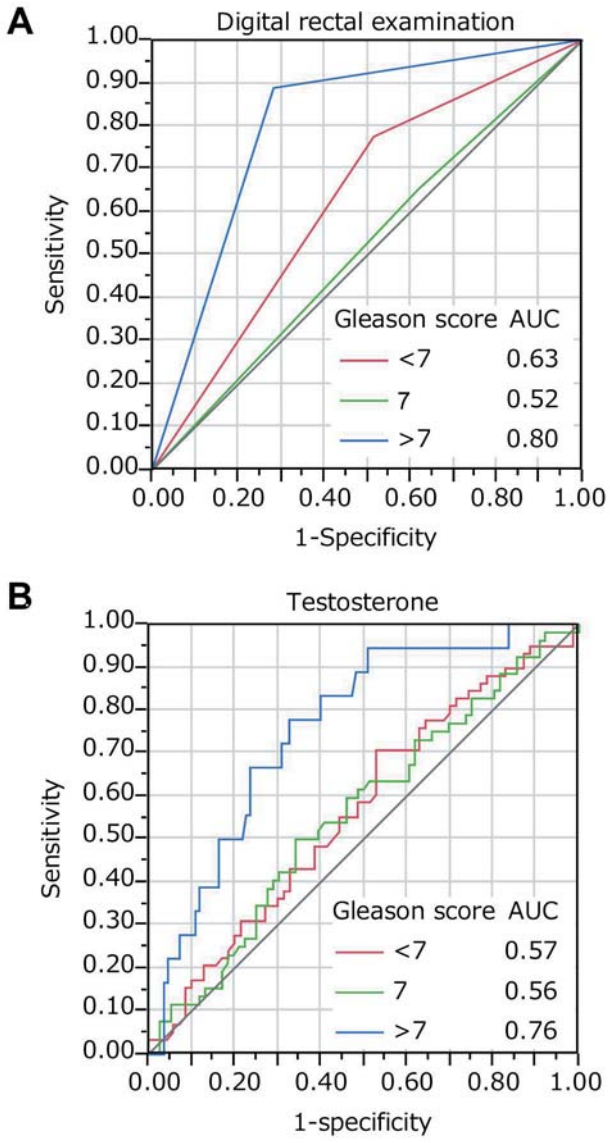

Figure 2. *Diagnostic value of digital rectal examination (DRE) findings and serum testosterone level for the prediction of Gleason score at biopsy. Receiver operator characteristic curves of DRE finding (A) and serum testosterone level (B) for the prediction of Gleason score at biopsy are shown. The curves describe the association between sensitivity and specificity.*

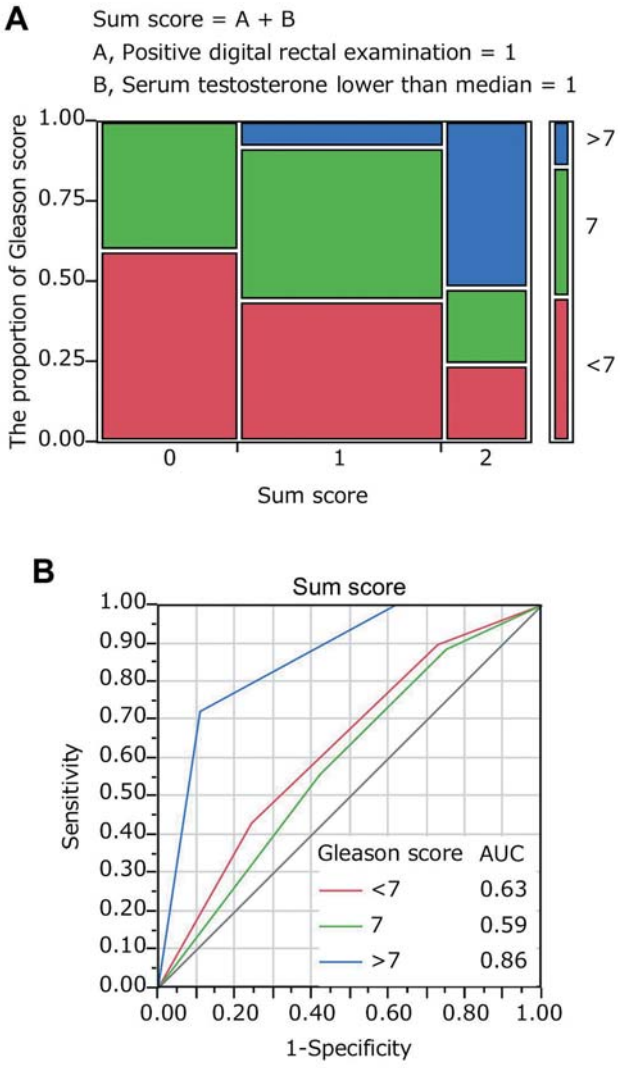

Figure 3. *Associations between the sums of scores calculated from digital rectal examination (DRE) finding and serum testosterone level and Gleason score at biopsy. A: Positive DRE finding and serum testosterone lower than the median were scored as 1 and then summed. The association between the sum score calculated from DRE finding/serum testosterone level and Gleason score at biopsy is indicated. B: Receiver operator characteristic curves of sum score for the prediction of Gleason score at biopsy. The curve describes the association between sensitivity and specificity.*

Obesity has also been associated with Gleason score (10, 24). However, similar to other reports for European and Japanese populations (11, 12), this study failed to show a significant correlation between BMI and Gleason score, further contributing to controversies in the relationship between obesity and Gleason score. The prevalence of obesity varies among ethnic groups, with a higher rate in the US, a a medium rate in Europe and lower rate in Asian countries (25). Therefore, this ethnic difference in obesity prevalence might affect the impact of BMI on the prediction of Gleason score, in addition to differences in study method and design.

A recent study from Germany that mainly included European Caucasians and investigated the impact of both serum testosterone level and BMI on clinicopathological characteristics demonstrated that BMI, but not serum testosterone level, correlated with high-grade and high-stage

Table III. *Concordance between Gleason score at biopsy and radical prostatectomy.*

Variable (n=28)	
Median age (IQR), years	65 (60-70)
DRE, n (%)	
Palpable	10 (35.7%)
Non-palpable	18 (64.7%)
Clinical stage, n (%)	
cT1	15 (62.5%)
cT2	8 (33.3%)
cT3	1 (4.2%)
NA	4
Median PSA at diagnosis (IQR), ng/ml	9.0 (6.4-11.5)
Surgical procedure, n (%)	
RRP	19 (67.9%)
LRP	7 (25.0%)
RALP	2 (7.1%)
Gleason score at biopsy, n (%)	
<7	10 (35.7%)
7	15 (53.6%)
>7	3 (10.7%)
Gleason score at RP, n (%)	
<7	3 (10.7%)
7	23 (82.1%)
>7	3 (10.7%)
Gleason score at radical prostatectomy, n (%)	
Down-grading	3 (10.7%)
Constant	16 (57.1%)
Up-grading	9 (32.1%)

IQR, Interquartile range; DRE, digital rectal examination; NA, not available; PSA, prostate-specific antigen; RRP, retropubic radical prostatectomy; LRP, laparoscopic radical prostatectomy; RALP, robot-assisted laparoscopic radical prostatectomy.

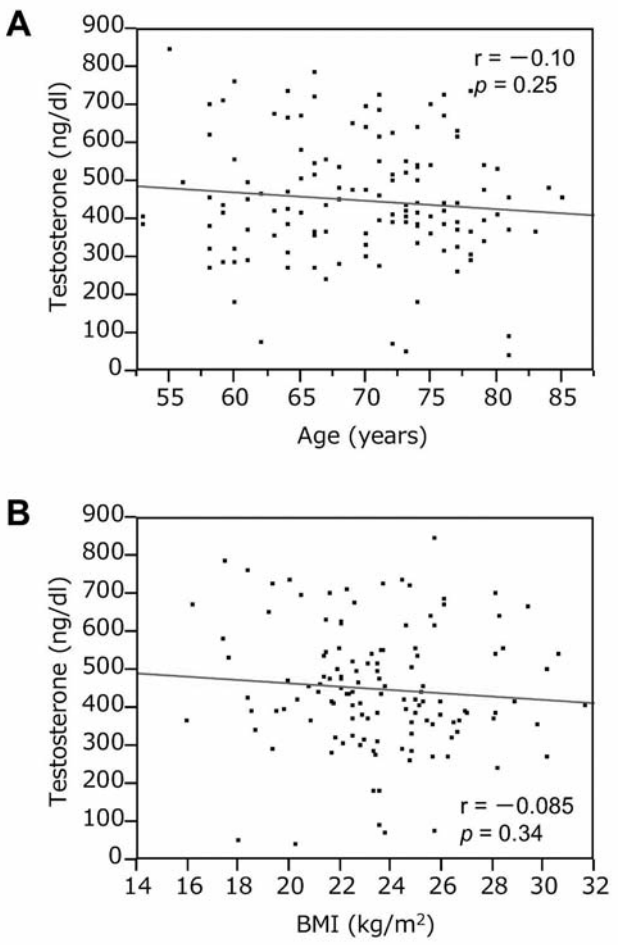

Figure 4. *Association of age (A) and body mass index (BMI) (B) with serum testosterone level.*

cancer (26). Notably, this study showed that serum testosterone, but not BMI, correlated with Gleason score. The inconsistency between our results may be due to ethnic differences and the differential prevalence of obesity (>30 kg/m^2), which was 18.2% in the European study (26) and only 3.1% in this study.

To determine appropriate therapeutics and predict prognosis, PSA level at diagnosis and clinical stage, as well as biopsy Gleason score, are critical factors. Recently, over-diagnosis and over-treatment of prostate cancer have become major issues since the establishment of PSA screening. Accordingly, active surveillance (AS) has been increasingly adopted for low-risk prostate cancer in order to avoid overtreatment. As indicated by several criteria of AS, a low PSA level at diagnosis, and low clinical T-stage as well as low Gleason score, are critical factors in determining whether prostate cancer can be managed by AS. However, a rate of reclassification as high as 30% may lead to loss of appropriate therapeutic intervention and is thought to be a major issue (27). Therefore, the serum testosterone level may help to select appropriate candidates for AS. A recent report showed that a low serum level of free testosterone was a predictor of disease reclassification by re-biopsy in men who underwent AS (28). Besides over-treatment, over-diagnosis is another problem in managing men with marginally abnormal serum PSA level of less than 20 ng/ml. Accordingly, the serum testosterone level may be helpful to determine whether men with a serum PSA level less than 20 ng/ml and non-palpable DRE findings should be biopsied.

In addition to serum testosterone level, several molecular biomarkers, such as human kallikrein 2, transforming growth factor-β1 and interleukin-6 receptor, and genetic biomarkers *BRCA*, *PTEN*, and *NKX3.1* have been suggested to be valuable in predicting aggressive high-grade cancer (29). Additionally, advances in radiological technology such as magnetic resonance imaging are also considered helpful to predict aggressive cancer (30). However, compared to these markers and techniques, serum testosterone measurement

Table IV. *Characteristics of 128 patients according to serum testosterone level*

Variable	Serum testosterone				*p*-Value
	Q1	Q2	Q3	Q4	
Median age (IQR), years	70 (62-76)	73 (64-76)	72 (65-76)	68 (63-73)	0.39
DRE, n (%)					
Palpable	13 (59.4%)	12 (37.5%)	11 (34.4%)	11 (34.4%)	
Non-palpable	19 (40.6%)	20 (62.5%)	21 (65.6%)	21 (65.6%)	0.95
Clinical stage, n (%)					
cT1	16 (57.1%)	14 (45.2%)	21 (67.7%)	19 (59.4%)	
cT2	7 (25.0%)	13 (41.9%)	7 (22.6%)	9 (28.1%)	
cT3	5 (17.9%)	4 (12.9%)	3 (9.7%)	4 (12.5%)	0.61
NA	4	1	1	0	
Median PSA at diagnosis (IQR), ng/ml	9.1 (6.6-13.5)	8.5 (6.7-10.9)	8.2 (6.4-11.8)	9.8 (6.5-12.0)	0.32
Q1, n (%)	8 (25.0%)	7 (21.9%)	8 (25.0%)	9 (28.1%)	
Q2, n (%)	6 (18.8%)	10 (31.3%)	10 (31.3%)	6 (18.8%)	
Q3, n (%)	8 (25.0%)	9 (28.1%)	6 (18.8%)	9 (28.1%)	
Q4, n (%)	10 (31.3%)	6 (18.8%)	8 (25.0%)	8 (25.0%)	0.91
Median BMI at diagnosis (IQR), kg/m2	23.6 (22.6-25.7)	24.0 (21.7-25.9)	22.6 (21.6-23.7)	23.1 (20.7-25.6)	0.51
Q1, n (%)	5 (15.6%)	8 (25.0%)	8 (25.0%)	11 (34.4%)	
Q2, n (%)	8 (25.0%)	7 (21.8%)	12 (37.5%)	5 (15.6%)	
Q3, n (%)	9 (28.1%)	7 (21.8%)	9 (28.1%)	7 (21.9%)	
Q4, n (%)	10 (31.3%)	10 (31.3%)	3 (9.4%)	9 (28.1%)	0.33

IQR, Interquartile range; NA, not available; DRE, digital rectal examination; PSA, prostate-specific antigen; BMI, body mass index.

would be a simple and convenient tool. Therefore, measuring serum testosterone alone, as well as in combination with these markers may increase its value in predicting high-grade cancer.

Numerous studies have investigated the relationship between male sex hormone and prostate cancer. Among them, the randomized control Prostate Cancer Prevention Trial (31) and REDUCE trial (32) examined the chemopreventative role of the 5α-reductase inhibitor finasteride and dutasteride, and showed that these agents reduced prostate cancer incidence but also increased the rate of aggressive cancer with high Gleason score, suggesting that a low androgen milieu induces an aggressive phenotype in prostate cancer. In line with these findings, low tissue levels of dihydrotestosterone, which is a more active metabolite of testosterone, has been reported in tissues with a high Gleason score (33), although the testosterone level in tissues was higher, suggesting low activity of 5α-reductase in tissues (34). Recently, Miyoshi *et al*. found that serum testosterone was not correlated with testosterone and dihydrotestosterone level in tissues (34), which is considered to reflect the prostate cancer microenvironment. Thus, although the mechanisms by which the androgen microenvironment promotes aggressive prostate cancer are complex, a low testosterone level does not appear to be a cause of aggressive prostate cancer. Conversely, prostate cancer with a high Gleason score may induce a lower serum testosterone level, as suggested by a previous study shaving that RP for aggressive prostate cancer restored testosterone levels to normal (35).

The present study had several limitations. The study design was retrospective and the sample size was relatively small. Additionally, a small proportion of tissue samples were diagnosed at other Institutions and not reviewed at our Institution. Nevertheless, this study shows a significant impact of serum testosterone on biopsy Gleason score. Previous studies showed that Gleason scores of biopsy and RP specimens may differ (36). In this study, Gleason score was determined by biopsy, which may differ from the true Gleason score determined from RP specimens. Additionally, this study included only Japanese men, which may limit the findings to Japanese populations. Moreover, the serum testosterone level, which is known to vary diurnally, was measured between 8:00 and 10:00 in this study. However, a previous study showed that serum testosterone in aged people was constant compared to that in younger populations (37), which may justify our approach and results.

Conclusion

This study showed that the pre-treatment serum testosterone level in addition to DRE findings, but not obesity, may be a predictive factor of biopsy Gleason score in Japanese patients. This finding is critical in helping to determine

appropriate interventions and predict prognosis for patients with prostate cancer. Thus, this study indicates the diagnostic value of DRE findings as well as serum testosterone in risk assessment in men with a marginally high serum PSA level, and in men with low-risk prostate cancer being treated with AS.

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