Asian Journal of Andrology (2020) 22, 323–329
www.asiaandro.com; www.ajandrology.com

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ORIGINAL ARTICLE

Prostate Cancer

High body mass index predicts multiple prostate cancer lymph node metastases after radical prostatectomy and extended pelvic lymph node dissection

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Our aim is to evaluate the association between body mass index (BMI) and preoperative total testosterone (TT) levels with the risk of single and multiple metastatic lymph node invasion (LNI) in prostate cancer patients undergoing radical prostatectomy and extended pelvic lymph node dissection. Preoperative BMI, basal levels of TT, and prostate-specific antigen (PSA) were evaluated in 361 consecutive patients undergoing radical prostatectomy with extended pelvic lymph node dissection between 2014 and 2017. Patients were grouped into either nonmetastatic, one, or more than one metastatic lymph node invasion groups. The association among clinical factors and LNI was evaluated. LNI was detected in 52 (14.4%) patients: 28 (7.8%) cases had one metastatic node and 24 (6.6%) had more than one metastatic node. In the overall study population, BMI correlated inversely with TT (r = –0.256; P < 0.0001). In patients without metastases, BMI inversely correlated with TT (r = –0.282; P < 0.0001). In patients with metastasis, this correlation was lost. In the overall study population, BMI (odds ratio [OR] = 1.268; P = 0.005) was the only independent clinical factor associated with the risk of multiple metastatic LNI compared to cases with one metastatic node. In the nonmetastatic group, TT was lower in patients with BMI >28 kg m^{-2} (P < 0.0001). In patients with any LNI, this association was lost (P = 0.232). The median number of positive nodes was higher in patients with BMI >28 kg m^{-2} (P = 0.048). In our study, overweight and obese patients had a higher risk of harboring multiple prostate cancer lymph node metastases and lower TT levels when compared to patients with normal BMI.

Asian Journal of Andrology (2020) **22**, 323–329; doi: 10.4103/aja.aja_70_19; published online: 26 July 2019

Keywords: body mass index; metastatic prostate cancer; multiple lymph node invasion; overweight-obesity; preoperative testosterone level

INTRODUCTION

A body mass index (BMI) >25 kg m^{-2} identifies overweight or obese patients and has been associated with different cancers, poor treatment outcomes, and increased cancer-specific mortality.[1] In the past 30 years, the prevalence of prostate cancer (PCa) has mirrored the spread of obesity and metabolic syndrome.[2,3] Many studies have identified the direct association between obesity and more aggressive PCa biology in terms of grade, stage, presence of metastasis, and PCa-related mortality. This association could be due to systemic obesity-related effects that result in increases of serum growth factors and pro-inflammatory cytokine levels.[4] Moreover, obesity influences the hypothalamus–pituitary–testis axis resulting in a reduction of systemic androgen levels, particularly in middle aged men.[5] The association between testosterone and prostate cancer was initially demonstrated by Huggins and Hodges who found that injections of testosterone in castrated PCa patients caused an increase in serum phosphatase.[6] In the last few years, the effect of variations in serum testosterone levels in middle aged men on PCa biology has been studied closely. Some evidence suggests that low testosterone levels are associated with more aggressive PCa, but other authors found a linear correlation between preoperative testosterone levels and more aggressive disease.[7] One measurable index of PCa aggressiveness is lymph node invasion (LNI). Extended pelvic lymph node dissection (ePLND) is the most effective method to detect LNI. Appropriate staging allows for more precise prognostication, and it may help guide postsurgical follow-up and selection of either adjuvant or salvage therapies.[8]

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Received: 27 December 2018; Accepted: 15 May 2019

In this study, we aim to assess the association between preoperative BMI and preoperative serum total testosterone (TT) levels with multiple LNI in PCa patients undergoing radical prostatectomy (RP) and ePLND.

MATERIALS AND METHODS

Study population

This study is a retrospective analysis of prospectively collected data. The institutional review board approval of the Azienda Ospedaliera Universitaria Integrata of Verona was obtained, and each patient provided informed-signed consent for data collection and analysis. Between November 2014 and December 2017, preoperative basal levels of serum TT and PSA were measured in 361 consecutive Caucasian patients undergoing RP and concomitant ePLND. No patient was under androgen deprivation therapy.

Clinical features

Serum samples of TT and PSA were obtained from a cubital vein, at 8.00–8.30 a.m. at least 1 month after prostate biopsy. All blood samples were analyzed by medical laboratory, and plasma levels of TT (ng dl^{-1}) and PSA (ng ml^{-1}) were determined by radioimmunoassay. Age (year), BMI (kg m^{-2}), prostate volume (PV, ml), biopsy positive cores (BPC; proportion), and biopsy grade group (BGG) were calculated for each case.

In our institution, the 14-core transperineal ultrasound-guided prostate biopsy technique was used. Prostate volume (ml) was measured with the formula for an ellipsoid during the ultrasound examination: d1 (height) × d2 (width) × d3 (length) × 0.52 (d: diameter). Biopsies performed elsewhere were assessed for the following features: (i) at least 12 biopsy cores; (ii) number of positive cores; and (iii) measurement of prostate volume.

In each case, clinical pelvic lymph node staging (cN) was performed by axial imaging modalities. Enlarged pelvic nodes measuring more than 1 cm in diameter were staged as cN1 disease. The metastatic status was investigated by both axial imaging and total bone scan modalities. Patients were staged according to the 2010 American Joint Committee on Cancer (AJCC) staging system for PCa (7th edition).[9]

According to the D'Amico risk classification, patients were divided into low-, intermediate-, and high-risk PCa groups.[10]

Perioperative features

In all high-risk patients, ePLND was performed. In the intermediate-risk patients, the decision to perform an ePLND was mainly based on preoperative nomograms showing a risk of lymph node invasion greater than 5%.[11] In low-risk patients, the decision to perform an ePLND was based on clinical factors indicating increased risk of tumor upgrading and LNI in the surgical specimen.[12,13]

Skilled and experienced surgeons performed RP with ePLND with either robot-assisted (RARP) or open retropubic (RRP) approaches. RARP was carried out using the da Vinci Robot Surgical System (Intuitive Surgical, Inc., Sunnyvale, CA, USA) and was performed through the transperitoneal approach with anterograde prostatic dissection.[14] RRP was performed according to the Walsh technique.[15] The lymph node dissection template included bilaterally external iliac (until the crossing of the ureter and the external iliac artery), Cloquet's, obturator, and Marcille's lymph node packets.

Pathological features

A dedicated pathologist examined RP specimens, which were processed according to the Stanford protocol.[16] International Society of Urological Pathology (ISUP) grade group system was applied to classify tumors.[17] Surgical margins were reported as positive when cancer invaded the inked surface of the specimen. Nodal packets were grouped into left and right and were tagged and submitted in separate containers. Lymph nodes were assessed for histopathology after hematoxylin and eosin staining. Immunohistochemical staining was performed when appropriate. In each case, the number of removed lymph nodes and LNI was reported. Prostate and nodal specimens were then staged according to the 2010 AJCC staging system for PCa.[9] Extraprostatic disease in the surgical specimen was defined as the presence of any of the following: extracapsular extension, positive surgical margins, seminal vesicle involvement, or LNI.

Statistical methods

Patients were divided into three groups according to the pathologic node status, which were defined as no metastatic lymph nodes, one metastatic node, or more than one metastatic node. Summary statistics and distributions of factors among groups were assessed. Data on continuous variables were reported as median and interquartile range (IQR), and differences among groups were analyzed by the Kruskal–Wallis test. Data on categorical variables were presented as frequencies with percentages, and differences among groups were analyzed with the Pearson's Chi-squared test or Fisher's exact test as appropriate. The multinomial logistic regression model (univariate and multivariate analysis) was used to evaluate the association between significant clinical factors and the risk of one or more than one metastatic node compared to no LNI. Moreover, cases with more than one metastatic node were also compared with patients having only one positive node. The correlation of BMI and TT with other clinical factors was evaluated among groups by Pearson's correlation coefficient (r of Pearson). Finally, patients were divided into two groups: patients with and without LNI, and both groups were stratified by the third quartile of BMI. Associations of BMI and TT between groups were investigated. The software used to run the analysis was IBM-SPSS version 20 (SPSS Inc., IBM Corp., Armonk, NY, USA). All tests were two-sided with $P < 0.05$ considered statistically significant.

RESULTS

In the general population, median age, BMI, TT serum level, and PV were 65 years, 25.3 kg m^{-2}, 422 ng dl^{-1}, and 40 ml, respectively. Clinically, 19 (5.3%) tumors were staged as >cT2, and LNI was suspected in 20 (5.5%) patients. Ninety (24.9%), 187 (51.8%), and 84 (23.3%) patients had low-, intermediate-, and high-risk disease by the D'Amico classification, respectively. RARP was performed in 297 (82.3%) cases and RRP in 64 (17.7%) patients (**Table 1**).

In the surgical specimen, low-grade tumors (ISUP Group 1) were found in 26 (7.2%) cases while intermediate-grade (ISUP Group 2–3) and high-grade cancers (ISUP Group 4–5) were found in 204 (56.5%) and 131 (36.3%) patients, respectively. pT3 stage was present in 112 (31.0%) cases, pT3a in 47 (13.0%) patients, and pT3b in 65 (18.0%) patients. Positive surgical margins were detected in 111 (30.7%) patients. The median number of nodes harvested was 26 (IQR: 20–33). The distribution of median number of nodes harvested did not differ among low-, intermediate-, and high-grade groups. Overall, LNI was detected in 52 (14.4%) patients, including 28 (7.8%) cases having one node with LNI and 24 (6.6%) patients with more than one metastatic node (**Table 1**).

Among clinical factors, significant statistical differences in median BMI, PSA, and BPC as well as the distribution of BGG among the three groups were detected. Specifically, patients with any LNI had higher median BMI, PSA, and BPC as well as higher rates of high-grade tumors on biopsy when compared with patients without LNI (**Table 1**).

Table 1: Demographics of the population and subgroups of patients who underwent extended pelvic lymph node dissection

	Overall population	*Lymph node invasion*			*P*
		Absent	*One node*	*> one node*	
n (%)	361	309 (85.6)	28 (7.8)	24 (6.6)	
Age (year)	65 (61–70)	65 (61–70)	66.5 (62–70)	65.5 (59–70)	0.94
BMI (kg m^{-2})	25.3 (23.6–28.1)	25.4 (23.6–28.1)	24.6 (22.4–26.2)	27.2 (24.2–28.1)	0.024
PSA (ng ml^{-1})	7.0 (5.1–9.7)	6.8 (5.1–8.9)	7.4 (5.1–10.9)	11.9 (4.9–20.6)	0.012
TT (ng dl^{-1})	422.0 (330.5–519)	422.1 (329.0–525.4)	444.0 (358.7–535.9)	396.5 (323.4–474.7)	0.399
PV (ml)	40.0 (30.0–53.0)	40.0 (30.0–51.5)	45.0 (29.0–61.5)	44.0 (36.5–59.7)	0.159
BPC (%)	38.0 (25.0–57.0)	33.0 (21.0–50.0)	50.0 (30.5–74.0)	59.0 (43.0–77.7)	<0.0001
cT, *n* (%)					
1	190 (52.7)	165 (53.4)	10 (35.7)	15 (62.5)	0.208
2	152 (42.1)	128 (41.4)	17 (60.7)	7 (29.2)	
3	19 (5.3)	16 (5.2)	1 (3.6)	2 (8.3)	
cN, *n* (%)					
0	341 (94.5)	293 (94.8)	27 (96.4)	21 (87.5)	0.286
1	20 (5.5)	16 (5.2)	1 (3.6)	3 (12.5)	
BGG, *n* (%)					
One	81 (22.4)	73 (23.6)	3 (10.7)	5 (20.8)	<0.0001
Two - three	202 (56.0)	181 (58.6)	15 (53.6)	6 (25.0)	
Four - five	78 (21.6)	55 (17.8)	10 (35.7)	13 (54.2)	
PW (g)	52 (42.5–50)	52 (41–64)	57 (43.5–74.5)	56 (47–70)	0.182
LN (*n*)	26 (20–33)	26 (19.5–32.5)	28.5 (22.2–36)	26.5 (22.2–32.7)	0.14
PGG, *n* (%)					
One	26 (7.2)	26 (8.4)	0 (0.0)	0 (0.0)	<0.0001
Two - three	204 (56.5)	191 (61.8)	8 (28.6)	5 (20.8)	
Four - five	131 (36.3)	92 (29.8)	20 (71.4)	19 (79.2)	
pT, *n* (%)					
2	249 (69.0)	229 (74.1)	13 (46.4)	7 (29.2)	<0.0001
3a	47 (13.0)	41 (13.3)	4 (14.3)	2 (8.3)	
3b	65 (18.0)	39 (12.6)	11 (39.3)	15 (62.5)	
SM, *n* (%)					
Negative	250 (69.3)	225 (72.8)	12 (42.9)	13 (54.2)	0.001
Positive	111 (30.7)	84 (27.2)	16 (57.1)	11 (45.8)	

BMI: body mass index; PSA: prostate-specific antigen; TT: total testosterone; PV: prostate volume; BPC: biopsy positive core; BGG: biopsy grade group; LN: lymph node; cT: clinical T stage; cN: clinical N stage; PW: prostate weight; PGG: pathological Gleason grade; pT: pathological T stage; SM: surgical margins status

Among pathologic factors, significant statistical differences in the distribution of tumor grade groups, pathologic stage, and surgical margin status were found. Patients with LNI showed significantly higher rates of high-grade tumors, seminal vesicle invasion, and positive surgical margins when compared to patients with no LNI. Patients with multiple metastatic LNI, when compared to the other two groups, showed higher median BMI and lower median TT levels; however, the difference was statistically significant only for BMI ($P = 0.024$, **Table 1**).

On univariate analysis, BPC (odds ratio [OR] = 1.022, 95% CI: 1.006–1.038; $P = 0.009$) and high BGG (OR = 4.424, 95% CI: 1.162–16.843; $P = 0.029$) were associated with the risk of one metastatic LNI when compared to negative cases. Moreover, BMI (OR = 1.136, 95% CI: 1.012–1.276; $P = 0.030$), PSA (OR = 1.077, 95% CI: 1.033–1.124; $P = 0.001$), BPC (OR = 1.038, 95% CI: 1.021–1.057; $P < 0.0001$), and high BGG (OR = 3.451, 95% CI: 1.161–10.255; $P = 0.026$) were associated with the risk of more than one metastatic node compared to negative cases. Finally, BMI (OR = 1.268, 95%CI: 1.076–1.495; $P = 0.005$) and PSA (OR = 1.078, 95% CI: 1.001–1.160; $P = 0.048$) were associated with an increased risk of having more than one metastatic node compared to cases having only one LNI (**Table 2**).

On multivariate analysis, only BPC (OR = 1.022, 95% CI: 1.006–1.038; $P = 0.009$) predicted the risk of one metastatic LNI compared to negative cases. In addition, PSA (OR = 1.056, 95% CI: 1.005–1.110; $P = 0.031$), BPC (OR = 1.027, 95% CI: 1.008–1.046; $P = 0.004$), and high BGG (OR 3.758, 95% CI: 1.512–9.456; $P = 0.005$) were predictors of harboring more than one metastatic lymph node when compared to patients without LNI. Finally, BMI (OR = 1.268, 95% CI: 1.076–1.495; $P = 0.005$) was the only independent clinical factor that was associated with the risk of multiple metastatic LNI compared to cases with one metastatic node (**Table 2**). **Figure 1** depicts the risk of more than one positive node when compared to BMI.

In the general population, BMI correlated inversely with TT ($r = -0.256$; $P < 0.0001$) and directly with PV ($r = 0.136$; $P = 0.010$). In the group of patients without LNI, BMI correlated inversely with TT ($r = -0.282$; $P < 0.0001$) and directly with PV ($r = 0.15$; $P = 0.008$). However, in the group of patients having LNI, BMI did not correlate with either TT or PV (**Table 3**). **Figure 2** depicts the correlation between BMI and TT in the general population. **Supplementary Figure 1** shows the correlation between BMI and TT in each subgroup.

Finally, the general population was divided into LNI and no LNI groups. The two groups were stratified by the third quartile of BMI (28 kg m^{-2}; **Table 4**). In the group without LNI, TT levels were lower in patients with BMI >28 kg m^{-2} compared to cases with

Table 2: Clinical factors associated with the risk of different patterns of lymph node invasion by the multinomial logistic regression analysis

Lymph node invasion	*One node versus none*			*More than one node versus none*			*More than one node versus one*		
	OR	*95% CI*	*P*	*OR*	*95% CI*	*P*	*OR*	*95% CI*	*P*
Univariate models									
BMI	0.896	0.792–1.013	0.080	1.136	1.012–1.276	0.030	1.268	1.076–1.495	0.005
PSA	1.000	0.935–1.069	0.995	1.077	1.033–1.124	0.001	1.078	1.001–1.160	0.048
BPC	1.022	1.006–1.038	0.009	1.038	1.021–1.057	<0.0001	1.016	0.994–1.039	0.150
BGG one	Reference			Reference			Reference		
BGG two - three	2.017	0.567–7.174	0.279	0.484	0.143–1.635	0.484	0.240	0.043–1.335	0.103
BGG four - five	4.424	1.162–16.843	0.029	3.451	1.161–10.255	0.026	0.780	0.150–4.069	0.057
Multivariate models									
BMI				1.093	0.962–1.243	0.171	1.245	1.053–1.471	0.010
PSA				1.054	1.001–1.140	0.044	1.076	0.998–1.161	0.057
BPC	1.020	1.004–1.037	0.016	1.027	1.008–1.046	0.006			
BGG one - three	Reference			Reference					
BGG four - five	2.310	0.996–5.356	0.051	3.564	1.407–9.030	0.007			
Final multivariate models*									
BMI							1.268	1.076–1.495	0.005
PSA				1.056	1.005–1.110	0.031			
BPC	1.022	1.006–1.038	0.009	1.027	1.008–1.046	0.004			
BGG one - three				Reference					
BGG four - five				3.758	1.512–9.456	0.005			

*Adjusted multivariate model. BMI: body mass index; PSA: prostate-specific antigen; BPC: biopsy positive cores; BGG: biopsy grade group; OR: odds ratio; CI: confidence interval

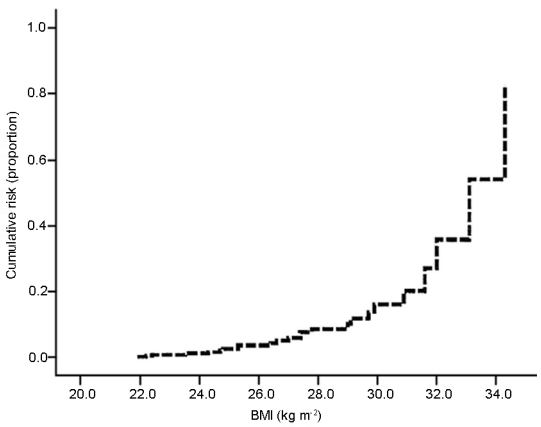

Figure 1: Correlation between BMI and the risk of more than one positive node. BMI: body mass index.

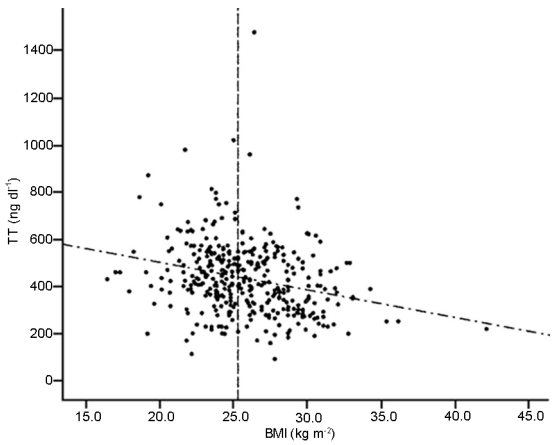

Figure 2: Correlation between BMI and preoperative TT serum levels in the general population. BMI: body mass index; TT: total testosterone.

BMI ≤28 kg m^{-2} (344.0 ng dl^{-1} *vs* 460.2 ng dl^{-1}; $P < 0.0001$). In the group with LNI, median TT levels were lower in patients with BMI >28 kg m^{-2} (390.0 ng dl^{-1}) than patients with BMI <28 kg m^{-2} (443.0 ng dl^{-1}), but did not reach statistical significance ($P = 0.232$). Moreover, the median number of positive nodes was significantly higher in patients with BMI >28 kg m^{-2} (two metastatic nodes) compared with cases having BMI ≤28 kg m^{-2} (one metastatic node) ($P = 0.048$).

DISCUSSION

PCa patients with LNI need further risk stratification because the metastatic burden is inversely correlated to disease specific survival.[8] In our study, 6.6% of cases had more than one metastatic lymph node and they represented 46.7% of LNI cases after RP. In patients with metastatic LNI, BMI was the only predictor of multiple LNI. Particularly, for each unit increase of BMI, we found a 27% increase in the risk of multiple LNI (OR = 1.268, $P = 0.005$) (**Figure 1** and **Table 2**). In the overall study population and in nonmetastatic cases, BMI was inversely associated with TT serum levels, but this association was lost in LNI patients.

In the last 30 years, the prevalence of PCa has mirrored the increase in obesity and metabolic syndrome.[2,3] For this reason, several studies have evaluated the relationship between visceral obesity (estimated through BMI) and PCa outcomes. De Nunzio *et al.*[18] found that obesity was associated with high-grade disease at the time of biopsy. Kelly *et al.*[19] suggested that increased BMI during adulthood results in an increased risk of fatal PCa. Jentzmik *et al.*[20] reported that obesity was significantly associated with high-grade and metastatic PCa. However, low levels of serum testosterone were not found to be associated with PCa. Freedland *et al.*[21] found that higher BMI was associated with biochemical recurrence after radical prostatectomy. In a recent meta-analysis, Gacci *et al.*[22] demonstrated that the presence of metabolic syndrome predicts aggressive PCa and biochemical recurrence after treatment. Further, we recently reported that increased BMI predicts the risk of high-grade complications after radical prostatectomy and ePLND.[23]

With respect to lymph node invasion, Pfitzenmaier *et al.*[24] found that BMI was not a predictor of adverse prognosis after radical

Table 3: Correlation of body mass index with other clinical factors in the population and subpopulations of patients who underwent extended pelvic lymph node dissection

Factors	*BMI*				
	Overall population	*No LNI*	*LNI*	*LNI (one node)*	*LNI (> one node)*
Age					
r	0.040	0.041	0.034	0.221	–0.108
P	0.445	0.469	0.812	0.250	0.615
PSA					
r	0.079	0.013	0.236	–0.062	0.195
P	0.134	0.822	0.092	0.752	0.362
TT					
r	–0.256	–0.282	–0.085	–0.026	0.003
P	<0.0001	<0.0001	0.551	0.895	0.990
PV					
r	0.136	0.150	0.059	–0.120	0.219
P	0.010	0.008	0.677	0.543	0.05
BPC					
r	0.033	0.008	0.146	–0.167	0.355
P	0.538	0.891	0.301	0.393	0.088

BMI: body mass index; LNI: lymph node invasion; PSA: prostate-specific antigen; TT: total testosterone; PV: prostate volume; BPC: biopsy positive core

Table 4: Associations of factors in patients with or without lymph node invasion stratified by the third quartile of body mass index of the patient population

	No lymph node invasion (n=309)			*Lymph node invasion (n=52)*		
	BMI ≤28 kg m^{-2}	*BMI >28 kg m^{-2}*	*P*	*BMI ≤28 kg m^{-2}*	*BMI >28 kg m^{-2}*	*P*
Patients (*n*)	230	79		39	13	
Age (year)	65 (61–70)	66 (61–70)	0.804	67 (62–70)	65 (59.5–68)	0.346
BMI (kg m^{-2})	24.3 (23.1–36.1)	29.7 (28.7–30.8)	<0.0001	24.7 (22.4–27.4)	30.5 (29.0–31.8)	<0.0001
PSA (ng ml^{-1})	6.6 (4.9–8.7)	7.2 (4.3–10.0)	0.177	7.8 (5.0–12.7)	12.4 (6.1–23.8)	0.148
TT (ng dl^{-1})	460.2 (367.7–548.0)	344.0 (277.8–438.0)	<0.0001	443.0 (358.2–508.4)	390.0 (318.0–471.5)	0.232
PV (ml)	38.7 (30.0–49.0)	42.9 (32.0–59.0)	0.015	45.0 (36.0–60.0)	45.0 (29.5–65.0)	0.916
BPC (%)	33 (21–50)	39 (25–57)	0.470	50 (35–71)	67 (50–100)	0.071
PGG, *n* (%)			0.065			0.714
One - three	168 (73.0)	49 (62.0)		9 (23.1)	4 (30.8)	
Four - five	62 (27.0)	30 (38.0)		30 (76.9)	9 (69.2)	
pT, *n* (%)						
2–3a	204 (88.7)	66 (83.5)	0.284	20 (51.3)	6 (46.2)	1.000
3b	26 (11.3)	13 (16.5)		19 (48.7)	7 (53.8)	
SM, *n* (%)						
Negative	169 (73.5)	56 (70.9)	0.655	19 (48.7)	6 (46.2)	1.000
Positive	61 (26.5)	23 (29.1)		20 (51.3)	7 (53.8)	
PW (g)	50.0 (40.0–62.0)	60.0 (48.0–70.6)	<0.0001	57.0 (46.0–70.0)	55.0 (43.5–74.0)	0.767
LN (*n*)	26 (20–33)	25 (19–32)	0.496	27 (22–36)	29 (22.5–41)	0.363
Positive lymph nodes (*n*)				1 (1–2)	2 (1–3.5)	0.048

BMI: body mass index; PSA: prostate-specific antigen; TT: total testosterone; PV: prostate volume; BPC: biopsy positive core; PGG: pathological Grade Group; pT: pathological T stage; SM: surgical margins status; PW: prostate weight; LN: lymph node

prostatectomy in 620 PCa patients. Particularly, the frequency of positive lymph nodes was not different between normal weight, overweight, and obese patients ($P = 0.58$). In that study, the authors did not specify the surgical approach, the number of dissected nodes, as well as the adopted template.[24] For this reason, it cannot be compared to the current study.

In overweight or obese patients, the risk of aggressive prostate cancer is related with systemic effects such as dyslipidemia and increased serum concentrations of inflammatory factors such as interleukin (IL)-6, IL-8, vascular endothelium grown factor (VEGF), and leptin, as well as the deregulation of the insulin/insulin-like growth factor-1 (IGF-1) axis. All these factors can harm the prostatic microenvironment and subsequently the cellular DNA. In addition, obesity has a pivotal role in altering the pituitary-testis axis in middle aged men, causing decreased serum TT levels through an increase in peripheral androgen aromatization.[4] Furthermore, obesity and other disease states may influence the concentration of sex hormone-binding globulin (SHBG)-bound testosterone and bioavailable testosterone, which is the sum of free testosterone (FT) and human serum albumin (HSA)-bound testosterone.[25]

Interestingly, Wang *et al.*[26] found that patients with an annual testosterone reduction of more than 30 ng dl^{-1} had an approximately 5-fold increase in PCa risk. They proposed that when a dramatic age-related decrease in serum testosterone occurs, local

autocrine-paracrine mechanisms attempt to maintain periprostatic testosterone concentrations by testosterone hyperproduction and androgen receptor (AR) hyperexpression. This results in an overall hyperstimulation of luminal glandular cells despite a decrease in TT serum levels, which, in turn, causes an increased prostatic cell stimulation that results in DNA damage and uncontrolled luminal cell AR-driven proliferation.[26] In addition, according to this hypothesis, recent evidence from the literature demonstrated that low baseline serum levels of FT are associated with an increased risk of high-grade PCa[27] as well as adverse pathologic features, functional outcomes, and biochemical recurrence.[28]

Theoretically, the simultaneous long-standing obesity and low systemic TT result in long-term cumulative prostate cell DNA damage and subsequent mutation. These alterations can constantly select newer and progressively more aggressive prostatic cellular clones. Initially, this process promotes neoplastic induction and cancer growth. Later, it provides progressive capacity for extracapsular diffusion, ability for nodal invasion, and, finally, the loss of hormonal sensitivity as is the case in castration-resistant PCa.[29–31]

These biological foundations can explain our results. We found that BMI is inversely associated with TT serum levels in the general and nonmetastatic LNI population, but this correlation lost statistical significance in metastatic patients. When we stratified LNI and non-LNI populations according to the third BMI quartile, a BMI >28 kg m^{-2} was associated with an increased risk of multiple LNI, but a BMI >28 kg m^{-2} had no correlation with TT levels. Probably, in our cohort, the patients with higher BMI have been exposed over a long period to the altered harmful cellular environment due to the simultaneous presence of obesity and low TT levels. This long exposure may provide the opportunity for multiple DNA mutations that may pave the way for LNI and castration resistance. Thus, increased BMI can be a predictive factor of multiple lymph node metastases in patients who undergo RP and ePLND as well as loss of androgen sensitivity. The association of BMI, PSA, serum TT, and BPC can help the clinician assess whether patients require more close postoperative oncological monitoring because of the increased risk of more aggressive disease.[32,33]

In our paper, we considered only TT serum levels, and we did not stratify TT into SHBG-bound testosterone and bioavailable testosterone. These markers may be altered by aging and disease states including obesity, liver disease, nephrotic syndrome, thyroid dysfunction, malnutrition, inflammatory and infectious conditions, and acute illness.[25] In this context, further prospective trials are needed in order to evaluate the relationship between metabolic and hormonal status and their effects on pathological and oncological outcomes in patients treated for PCa.

Our analysis has several limitations. First, prostate biopsies were not always performed in our institution, but specific confirmation criteria were used. Second, different surgeons performed RP and ePNLD, but all were skilled experts. Third, perirectal and internal iliac lymph nodes were not dissected. Harvesting these nodes has not been demonstrated to have a favorable risk advantage.[34] However, the median number of dissected nodes was appropriate to correctly compute the analysis. Fourth, as mentioned above, we evaluated only the TT baseline serum levels and we did not stratify it in SHBG-bound testosterone and bioavailable testosterone. Although scientific societies recommend testing more than one morning sample for serum TT, this protocol is used in the screening of hypogonadism or male hormonal diseases.[35,36] We used only one morning sample during the preoperative evaluation because many patients traveled to our tertiary center from far away only 1 day before surgery. For this reason, the collection of multiple consecutive daily blood samples was not feasible. Although serum TT levels in our patients should be interpreted in this context, we believe that our data were able to provide an adequate estimation of a patient's testosterone for the comparison with BMI and LNI.

To the best of our knowledge, our study is the first in modern literature that demonstrates direct correlation between BMI and multiple lymph node invasion that has a foundation in pathophysiologic science. Our results show that the presence of preoperative obesity can help predict the presence of lymph node invasion and stratify the risk of harboring aggressive prostate cancer. These patients require close postoperative monitoring in order to make therapeutic adjustments at the appropriate time.

Furthermore, we would like to highlight the importance of monitoring androgen levels and making healthy lifestyle choices in men. All scientific communities should influence the social policies of developed countries to promote more healthy alimentation regimes and hormonal screening in middle aged men.

In overweight and obese PCa patients undergoing RP and ePLND, the risk of multiple LNI is increased. The negative correlation between BMI and TT levels in nonmetastatic patients is lost in patients with LNI.

AUTHOR CONTRIBUTIONS

ABP provided the study design and conception, drafting of the manuscript, and carried out the statistical analysis. AT provided the study design, drafting of the manuscript, and analysis and interpretation of data. MS, MP, TP, NA, and RR carried out data collection. AS provided manuscript drafting, language revision, and critical revision. MB, MAC, SS, and WA provided supervision and critical revision of the manuscript for important intellectual contents. All authors read and approved the final manuscript.

COMPETING INTERESTS

All authors declared no competing interests.

Supplementary Information is linked to the online version of the paper on the *Asian Journal of Andrology* website.

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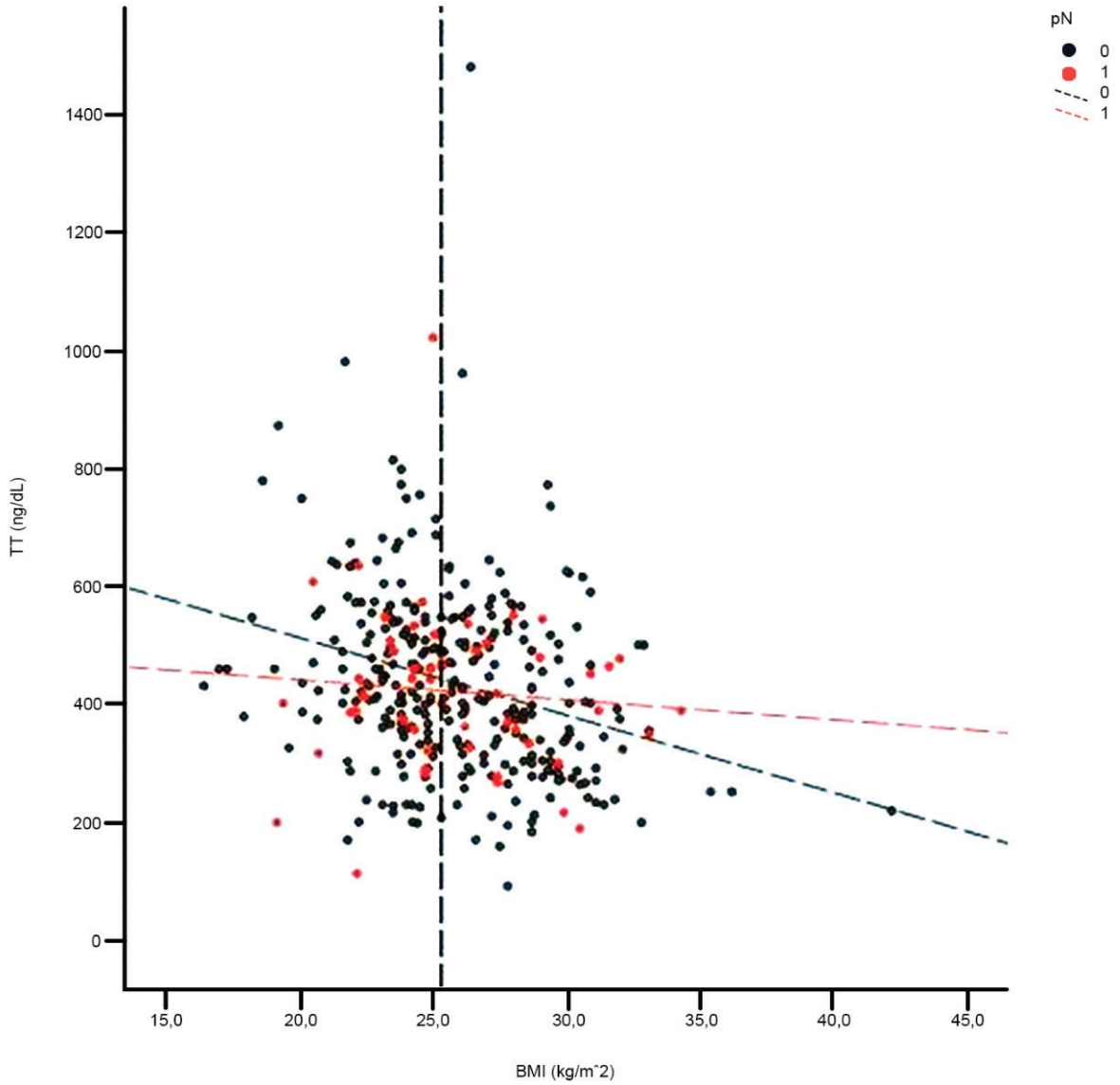

Supplementary Figure 1: Correlations between BMI and TT serum levels in patients with and without metastatic lymph nodes. TT: total testosterone; BMI: body mass index.