European Review for Medical and Pharmacological Sciences 2022; 26: 391-398

Risk factors of bone metastasis in patients with newly diagnosed prostate cancer

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Abstract. – OBJECTIVE: The current study aimed to explore the risk factors for bone metastasis (BMT) in patients with newly diagnosed prostate cancer (PCa).

PATIENTS AND METHODS: The clinical data of 322 patients newly diagnosed with PCa following transrectal prostate biopsy at our hospital from October 2016 to March 2021 were analyzed. According to the results of whole-body bone emission computed tomography (ECT) scanning, patients were divided into the following two groups: bone metastasis group (BMT) and none-bone metastasis group (None-BMT). Univariate and multivariate logistic regression analyses were performed to assess the BMT-related factors associated with PCa. A receiver operating characteristic curve was also used to compare the diagnostic value of total prostate-specific antigen (TPSA), prostate-specific antigen density (PSAD), Gleason score and alkaline phosphatase (ALP) for prostate cancer bone metastasis (PCBM).

RESULTS: The results revealed that the incidence of BMT in newly diagnosed patients with PCa was ~22.05% (71/322). Univariate analysis demonstrated that Gleason score, clinical T stage, TPSA, PSAD and ALP were associated with PCBM (p<0.001). Furthermore, the results of multivariate regression analysis revealed that TPSA, PSAD, Gleason score and ALP were independent risk factors for BMT (p <0.05). The cutoff values for TPSA, PSAD, ALP and Gleason score were 39.58 ng/ml, 1.489 ng/(ml/cm^3), 93.15 U/l and 7.5, respectively. Additionally, the respective sensitivities for TPSA, PSAD, ALP and Gleason score were 67.6, 62.0, 57.7 and 46.5%, and the respective specificities were 88.4, 98.0, 100 and 98.8%.

CONCLUSIONS: The current study determined that TPSA, PSAD, Gleason score and ALP were predictors of PCBM. In patients with PSA levels >39.58 ng/ml, PSAD levels >1.489 ng/(ml/cm^3), Gleason scores >7.5 and ALP levels >91.0 U/l, a whole-body bone ECT scan is recommended.

Key Words:
Bone metastasis, Prostate cancer, Risk factors, Prostate specific antigen, Specificity, Sensitivity.

Introduction

Prostate cancer (PCa) is the most common epithelial malignant tumor observed in men in Europe and the United States and is the second most common cause of cancer-related mortality[1]. The incidence of PCa in China is lower compared with that in developed countries, such as Europe and the United States; however, the incidence rate has been increasing rapidly in recent years, with >70% of patients with advanced PCa exhibiting bone metastasis (BMT)[2,3]. BMT causes bone metabolism disorders and triggers various skeletal related events (SREs), such as spinal cord compression, pathological fractures and hypercalcemia. These events not only reduce the quality of life of the patients, but also increase the socioeconomic burden and mortality rates[4,5]. The early detection of BMT is therefore of great importance, as it can dictate the available treatment options for PCa and the preventative measures for SREs.

PCa frequently develops distant metastases, of which BMT is the most common. Current clinical studies[6-8] have revealed that BMT rates are as high as 90% in patients with metastatic PCa. Unlike patients from Europe and America, certain patients with PCa from China have already developed distant metastases when they are first diagnosed[6-8]. Unfortunately, there are no factors that can accurately predict BMT in newly diagnosed patients with PCa[6-9]. Current research suggests that age, prostate-specific antigen (PSA), Gleason score, clinical stage and other indicators of PCa may have a degree of predictive value for BMT; however, a consensus on these factors has not yet been reached[10-12]. Therefore, the aim of the current study was to review the clinical data of 322 newly diagnosed patients with PCa and to explore the predictive value of patient age, body mass index (BMI), PSA levels, Gleason score, PSA density (PSAD), clinical stage and alkaline phosphatase (ALP) levels for BMT.

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Patients and Methods

Inclusion and Exclusion Criteria

A total of 322 patients with PCa who were newly diagnosed following transrectal prostate biopsy at our hospital from October 2016 to March 2021 were retrospectively analyzed. The inclusion criteria were as follows: i) pathologically confirmed prostate adenocarcinoma following transrectal ultrasound-guided prostate biopsy; ii) newly diagnosed cases that did not receive chemotherapy, radiotherapy or hormone therapy; and iii) no history of other malignant tumors. The exclusion criteria were as follows: i) the pathological diagnosis was not confirmed in a patient with PCa; ii) BMT being the result of other malignant tumors; iii) patients who had been treated with 5-α-reductase inhibitors for a long time prior to diagnosis; and iv) patients who had incomplete case data. All patients underwent whole body bone emission computed tomography (ECT) scanning after PCa diagnosis, with further CT and MRI examinations performed on suspicious lesions. According to the results of imaging, patients were divided into the following two groups: BMT (n=71) and non-BMT (n=251). The present study was reviewed and approved by the Ethics Committee of Chongqing Hospital of Traditional Chinese Medicine. All patients provided their written informed consent for participation in the current study.

Diagnostic Criteria of BMT

Whole body bone ECT scanning is an effective and non-invasive method for the diagnosis of BMT, with a sensitivity of 62-89%. Compared with X-rays, BMT can be detected 3-6 months earlier using whole body bone ECT, which is why this modality is widely used for the diagnosis of BMT[13-16]. The results of the ECT examinations of the current study were reviewed and approved by two senior and experienced nuclear medicine physicians. The diagnostic criteria for BMT were collated from previous literature and were as follows: i) patients exhibiting a local concentration of radioactivity that is higher compared with the healthy side or adjacent tissue, where false-positive factors such as bone degeneration or previous bone trauma were excluded; ii) patients exhibiting scattered radioactive foci in ≥2 locations; and iii) suspicious lesions on bone scans were diagnosed via CT and MRI[13-16].

Data Collection

The age, BMI, total PSA (TPSA) level, free PSA (FPSA) level, prostate volume, clinical stage, PSAD level, ALP level, Gleason score and other indicators of patients were recorded for statistical analysis. TPSA, FPSA and ALP were measured via chemiluminescence using the American Beckman Coulter Company Access automatic chemiluminescence immunoassay analyzer (Beckman Coulter, Inc.). The PHILIPS HD-11 GE-VOLUSION 730 EXEPERT color Doppler ultrasound diagnostic instrument (Philips Healthcare, Inc.) was also used to measure the anteroposterior, transverse and cephalocaudal diameters of the prostate. The total prostate volume was therefore determined according to the following formula: Prostate volume = (anteroposterior diameter x transverse diameter x cephalocaudal diameter) x $\pi/6$. Additionally, the PSAD value was calculated as follows: PSAD = PSA/prostate volume. The clinical T staging of PCa was performed according to the guidelines of the European Urological Association[17,18].

Statistical Analysis

The R software package was used for data processing. All data conforming to a normal distribution were presented as the mean ± SD, and all data that were non-normally distributed were presented as the median value. The comparison of normally distributed data between groups was performed using a *t*-test, while the comparison between non-normally distributed data was performed using a Mann-Whitney U test. The rate test was performed using χ^2. The association between each variable and PCa BMT was analyzed using univariate and multivariate logistical regression analyses. Receiver operating characteristic (ROC) curves were constructed using GraphPad prism 9.0 software (GraphPad Software, La Jolla, CA, USA), and utilized random forest analysis for statistical modeling. $p<0.05$ was considered to indicate a statistically significant difference.

Results

Comparative Analysis of Clinical Features Between the BMT and non-BMT Groups

The results of the present study revealed that the incidence of BMT in newly diagnosed patients with PCa was ~22.05% (71/322). In terms of age, significant differences were identified between the two groups of patients regardless of age grouping or overall age ($p<0.05$). As presented

Table I. Clinical characterize between prostate cancer with bone metastasis (BMT) and none bone metastasis (None-BMT).

Characterize		BMT (n=71)	None-BMT (n=251)	*p*-value
Age	<60	1 (0.31%)	31 (9.63%)	0.017
	60-69	25 (7.76%)	93 (28.88%)	
	70-80	37 (11.49%)	100 (31.06%)	
	≥81	8 (2.48%)	27 (8.39%)	
Gleason score	~6	7 (2.17%)	60 (18.63%)	<0.001
	7	31 (9.63%)	188 (58.39%)	
	8~	33 (10.25%)	3 (0.93%)	
TPSA	~10.0	6 (1.86%)	72 (22.36%)	<0.001
	10.1-20.0	9 (2.80%)	87 (27.02%)	
	20.1-100.0	34 (10.56%)	91 (28.26%)	
	100.0~	22 (6.83%)	1 (0.31%)	
fPSA/PSA	~0.16	43 (13.35%)	164 (50.93%)	0.548
	0.16~	28 (8.70%)	87 (27.02%)	
PSAD	0.01-0.15	2 (0.62%)	61 (18.94%)	<0.001
	0.16-0.20	0 (0%)	26 (8.07%)	
	0.21-0.50	8 (2.48%)	92 (2.86%)	
	>0.50	61 (18.94%)	72 (22.36%)	
Diabetes	Yes/No	10/61	31/220	0.853
Hypertension	Yes/No	27/44	65/186	0.064
Heart Disease	Yes/No	4/67	21/230	0.617
T stage	1/2/3/4	7/27/17/20	66/155/20/10	<0.001

in Table I and Figure 1, there were no significant differences between the two groups in terms of BMI, FPSA level, PSA level, diabetic status, hypertension status and heart disease occurrence (p<0.05). However, there were significant differences between Gleason scores (p<0.001), TPSA levels (p<0.001), PSAD levels (p<0.001), ALP levels (p<0.001) and clinical T stage (p<0.001).

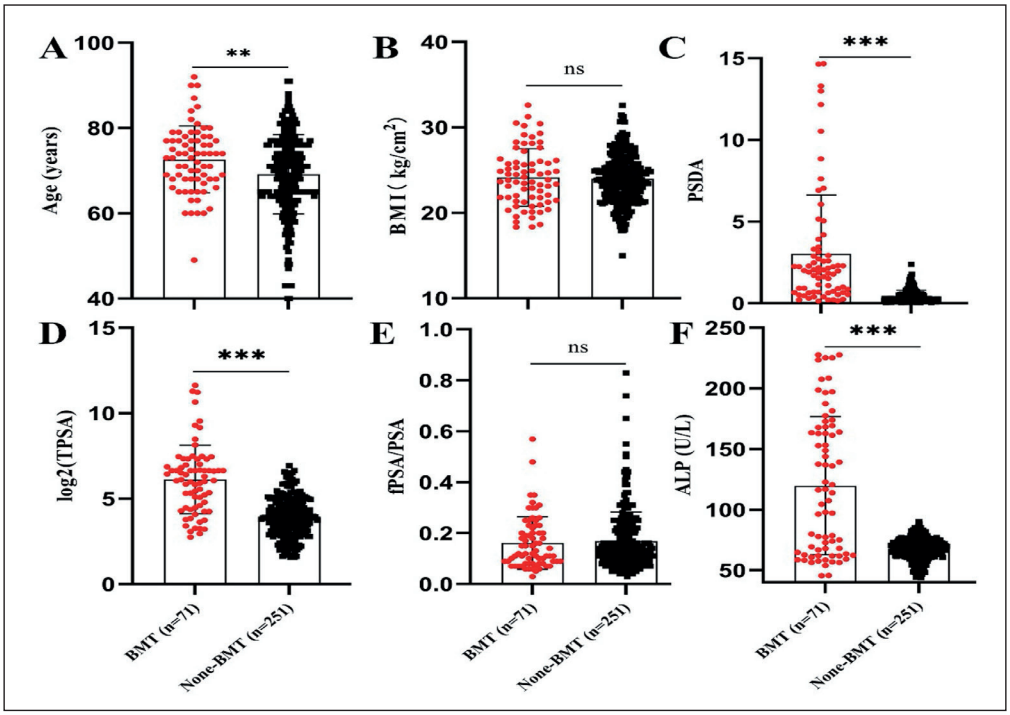

Figure 1. Comparison of Age **(A)**, BMI **(B)**, PSDA **(C)**, TPSA **(D)**, fPSA/PSA **(E)** and ALP **(F)** between prostate cancer with bone metastasis (BMT) and none bone metastasis (None-BMT).

Table II. Logistical regression analysis of clinical characterize influencing the development of bone metastasis in prostate cancer.

	Estimate Std.	Error	z value	Pr(>|z|)	95%CI
(Intercept)	-6.789828	3.247713	-2.091	**0.03656**	[-13.58, -0.74]
Age	0.009197	0.022948	0.401	0.68859	[-0.03, 0.06]
TPSA	0.001159	0.008541	0.136	**0.01892**	[-0.01, 0.02]
PSDA	1.899634	0.620984	3.059	**0.00222**	[0.71, 3.16]
ALP	0.022623	0.010371	2.181	**0.02916**	[0.01, 0.05]
T stage	-0.319827	0.308007	-1.038	0.29901	[-0.94, 0.27]
Gleason score	0.302449	0.429493	0.704	**0.01411**	[-0.51, 1.19]

Table III. Analysis of sensitivity and specificity between TPSA, PSA, PSAD and Gleason score and bone metastasis of prostate cancer.

	Cutoff	Specificity	Sensitivity	AUC	95%CI
TPSA	39.58	0.884	0.676	0.828	0.767-0.888
PSDA	1.489	0.98	0.62	0.877	0.827-0.927
ALP	93.15	100	0.577	0.731	0.644-0.817
Gleason score	7.5	0.988	0.465	0.743	0.668-0.818

Multivariate Logistical Regression Analysis of Risk Factors for BMT

As presented in Table II, multivariate logistical regression analysis revealed that TPSA [95% confidence interval (CI), -0.01-0.02; p=0.01892], PSDA (95% CI, 0.71-3.16; p=0.00222), ALP (95% CI, 0.01-0.05; p=0.02916) and Gleason score (95% CI, -0.51-1.19; p=0.01411) were independent risk factors for BMT in newly diagnosed patients with PCa.

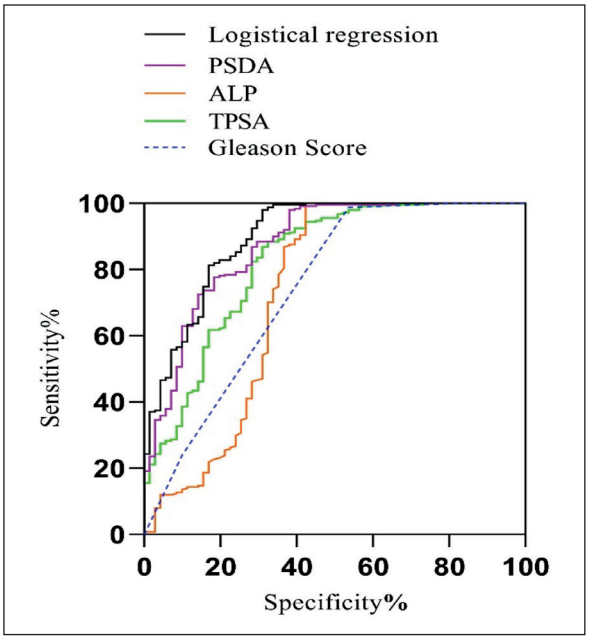

Figure 2. ROC curve of clinical characterize in predicting the development of bone metastasis in prostate cancer.

ROC Curve, Cut-Off Value, Sensitivity and Specificity Analysis of TPSA, PSAD, ALP, Gleason Score and BMT

As presented in Table III and Figure 2, the area under the TPSA curve was 0.828. When the optimal critical value was 39.58 ng/ml, the calculated sensitivity was 67.6% and the specificity was 88.4%. The area under the PSAD curve was 0.877, and when the optimal critical value was set to 1.48 ng/(ml/cm^3), the calculated sensitivity was 62.0% and the specificity was and 98.0%. Additionally, the area under the curve of ALP was 0.731. When the optimal critical value was set to 91.0 U/l, the calculated sensitivity was 57.7% and the specificity was 100.0%. The area under the Gleason score curve was 0.743, and when the optimal critical value was set to 7.5, the calculated sensitivity was 46.5% and the specificity was 98.8%.

Random Forest Model for Risk Factors of BMT

Random forest is as a classification algorithm that was employed for data analysis in the current study. The classification accuracy of the random forest method depends on the user-defined parameters, N and m. In the current study, N was set to 50 and m was set 1 to assess optimal prediction effects in patients with PCa exhibiting advanced BMT. The OOB estimate of error rate was set to 0.08 and was used to measure variant importance in patients with PCa exhibiting advanced BMT. Mean decreased accuracy and Gini results are presented in Figure 3A and 3B, where the level of

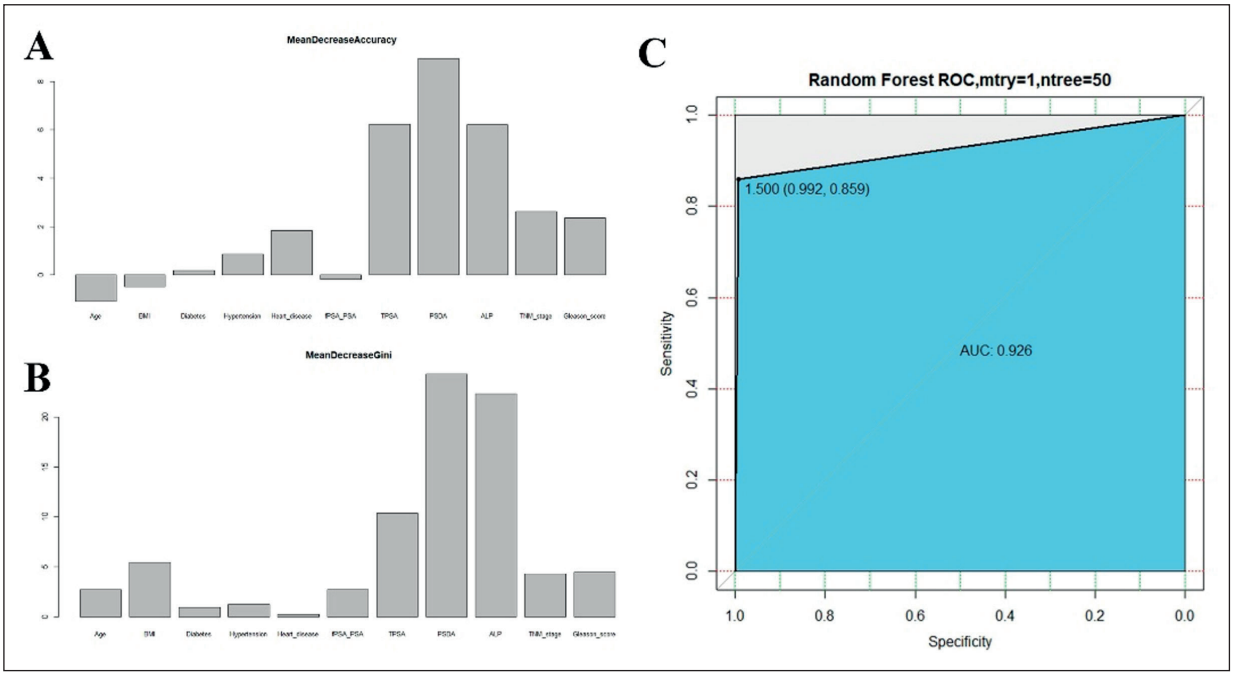

Figure 3. The using of random forest model in predicting the development of bone metastasis in prostate cancer. Average decreased accuracy **(A)** and Gini **(B)** in the model, and ROC curve **(C)** of random forest predicting score.

PSDA was determined to be the most important variant for detecting PCa with advanced BMT. The analysis further revealed that, at the optimal cut-off value of 1.5 for the random forest model, the sensitivity was 99.2% and the specificity was 85.9%, with an area under the curve value of 0.926 (95% CI, 0.89-0.94; Figure 3C).

Discussion

A study[19] reported that the incidence of BMT in newly diagnosed patients with PCa was 2.8%. However, in China, due to the relatively weak medical and health awareness of patients and the fact that PSA screening is far less popular than in Western countries, a number of patients with PCa already exhibit BMT when they first seek medical assistance[2,20]. Chien et al[21] determined that the incidence of BMT in newly diagnosed patients with PCa in Taiwan was ~19.0%. The results of the present study revealed that the incidence of BMT in newly diagnosed patients with PCa in China was ~22.05% (71/322). This result indicates that the incidence of BMT in patients with PCa in China is relatively high, meaning that there is an urgent need to raise public health awareness and design a suitable PSA screening system.

PCa often results in BMT, which in turn, causes various SREs, including bone pain at the metastatic site, pathological fractures and spinal cord compression. These conditions seriously affect the quality of life and prognosis of patients with PCa[22,23]. Therefore, it is very important for newly diagnosed patients with PCa to elucidate whether BMT has occurred, and to adopt corresponding treatment measures to improve their overall survival rate and improve or delay the occurrence of SREs. Studies[24,25] have demonstrated that the incidence of PCa increases with age. Merdan et al[25] studied 416 cases of PCa and determined that the rate of BMT was 11.8%, with the median age of BMT incidence occurring at 68.2 years. In the current study, the age of patients with PCa exhibiting BMT was significantly higher compared with that in patients without BMT. Furthermore, the probability of PCa BMT may increase with age, and BMT accounted for 63.3% of patients aged >70 years. However, multivariate regression analysis revealed that age was not an independent predictor of BMT. The current results therefore did not conclusively indicate that advanced age was associated with a higher incidence of PCa BMT.

Previous studies[26-28] have demonstrated that, when PSA levels are >100 ng/ml, the probability of BMT reaches 41.4-79.9%, and that when PSA levels are <20 ng/ml, the probability of

BMT is greatly reduced. The American Joint Committee on Cancer recommends that patients with PCa that exhibit PSA levels >20 ng/ml or a biopsy Gleason score >7 should undergo bone scans[29]. However, the European Association of Urology has proposed that bone scans should not be performed for patients with PCa with PSA <20 ng/ml and whose tumors are moderately or well-differentiated[30]. The results of the current study revealed that the TPSA level of the BMT group was significantly higher compared with that of the non-BMT group (p<0.001). Both univariate and multivariate regression analyses also demonstrated that TPSA was an independent associated factor of PCa BMT, and had a predictive effect on its occurrence. In addition, the present data suggested that an appropriate cutoff value for PSA was 39.58 ng/ml, meaning that patients with PCa with PSA levels >39.58 ng/ml have a higher risk of developing BMT, with a sensitivity of 67.6% and a specificity of 88.4%.

Serum PSA exists in free (FPSA) and bound states, with the former accounting for 10-30% of TPSA. Studies[31-33] have reported that PSAD and FPSA/TPSA can be used to distinguish between benign prostatic hyperplasia and PCa, demonstrating a potential value in judging the degree of PCa malignancy. The present study revealed that there was no statistical difference in FPSA/PSA values between the BMT group and the non-BMT group; however, PSAD was significantly higher in the BMT group compared with the non-BMT group (p<0.001). The results of regression analysis suggested that PSAD was an independent risk factor and predictor of PCa BMT. The cutoff value for PSAD was 1.489, with a sensitivity of 62.0% and a specificity of 98.0%.

Previous studies[34,35] have demonstrated that PCa BMT in patients with a high T stage is associated with a wide range of cancer lesions, a poor prognosis and a high Gleason score. The results of the current study revealed that a significantly higher number of patients in the BMT group had a high T stage compared with the non-BMT group (p<0.001). However, multivariate regression analysis demonstrated that a high clinical T stage was not a risk factor for PCa BMT. The possible reason behind this result may be that other risk factors, such as PSA levels, PSDA levels, Gleason score and ALP levels, may outweigh high clinical T stage as a potential risk factor. On the basis of previous clinical experience, the authors recommend that medical professionals assessing patients with a high clinical T stage must first determine whether the patient has BMT. The Gleason scoring system is currently the most commonly used method for grading PCa. It has become one of the most effective indicators for tumor staging and the evaluation of distant metastasis, patient prognosis and the scope of tumor invasion[36-39]. Previous studies[36-39] have indicated that, if a patient with advanced PCa has a Gleason score >7, they often exhibit local tumor infiltration or BMT. The current study demonstrated that a significantly increased number of patients in the BMT group exhibited a Gleason score >7 compared with the non-BMT group (p<0.001). Regression analysis confirmed that Gleason score was an independent factor and predictor of PCa BMT. The cutoff value for Gleason score was 7.5, with a sensitivity of 46.5% and a specificity of 98.8%. This result suggested that patients with PCa with a Gleason score >7 are at an increased risk of developing BMT, meaning that clinical attention is required.

ALP is a monolipid phosphohydrolase that is closely associated with bone metabolism and reflects osteogenic activity. Previous studies have revealed that ALP can be used as an effective indicator for the diagnosis of PCa BMT after excluding the presence of hepatic and benign bone lesions[40,41]. Studies[42,43] have also determined that serum ALP levels are positively associated with the results of bone imaging, where the degree of ALP increase is closely associated with BMT severity of BMT. Retrospective analysis has demonstrated that patients with PCa that suffer from bone pain also have serum ALP levels (>90 U/l), suggesting that BMT may have occurred[43]. The univariate and multivariate regression analyses in the present study confirmed that ALP was an independent risk factor and predictor of PCa BMT. The cutoff value for ALP was 93.15 U/l, with a sensitivity of 57.7% and a specificity of 100.0%.

There were certain limitations to the present study. The study was retrospective in nature, and this study design is associated with inherent limitations and biases. Additionally, the present research was conducted in a single center laboratory with only a small sample size, and therefore its conclusions must be interpreted with caution. Inherent errors and biases also exist in the experimental results due to the differences in race, living environment and medical conditions of patients included in the current study,

Conclusions

The current study revealed that PSA, Gleason score, PSAD and ALP were significantly associated with PCa BMT and represented independent risk factors of the disease. When PSA levels are >39.58 ng/ml, PSAD levels are >1.489, Gleason scores are >7.5 and ALP levels are >93.15 U/l, these factors demonstrate predictive value for BMT in patients with PCa.

Conflict of Interests

The authors declare that they have no conflict of interest.

Acknowledgments

This work was supported by Joint Project of Science and Health in Chongqing, Fund No. 2018QNXM005.

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