Am J Transl Res 2023;15(2):1502-1509
www.ajtr.org /ISSN:1943-8141/AJTR0147841

Original Article

Establishment and validation of a predictive model for bone metastasis in prostate cancer patients based on multiple immune inflammatory parameters

Zhigang Wang, Yi Sun, Wei Ren, Zhenfeng Guan, Ji Cheng, Xinqi Pei, Qingchuan Dong

Urology Surgery, Shaanxi Provincial People's Hospital, Xi'an 710068, Shaanxi, China

Received November 18, 2022; Accepted January 18, 2023; Epub February 15, 2023; Published February 28, 2023

Abstract: Objective: This study aims to establish and validate a predictive model for bone metastasis in prostate cancer patients based on multiple immune inflammatory parameters. Methods: In this retrospective study, 162 prostate cancer patients who met the inclusion criteria were selected by Urology Surgery, Shaanxi Provincial People's Hospital. Based on the medical record number of patients and the random number table method, 40 patients were randomly included in a validation group, and the rest were in a modeling group. The patients in the modeling group were divided into a metastatic group (n=67) and a non-metastatic group (n=55) according to the whole-body bone imaging results. Results: The predictive model was established based on the results of Logistics regression analysis: Logit (P) = -5.341 + 0.930*total Gleason score + 1.426*total prostate specific antigen + 0.836*neutrophil-lymphocyte ratio + 0.896*platelet lymphocyte ratio + 0.641*lymphocyte/monocyte ratio + 0.750*albumin/globulin ratio. ROC analysis showed that the areas under the curve of the predictive model for bone metastasis in the modeling and validation groups were 0.896 and 0.870, respectively. Hosmer-Lemeshow test showed that P=0.253, indicating a high degree of the fitting. External verification results showed that the C-index for predicting prostate cancer bone metastasis in the predictive model established in this study was 0.760 (95% CI: 0.670-0.851). Conclusion: The bone metastasis predictive model based on the multiple immune inflammatory parameters (neutrophil-lymphocyte ratio, platelet lymphocyte ratio, lymphocyte/monocyte ratio and albumin/globulin ratio) in prostate cancer patients can reasonably predict the occurrence of bone metastasis and is well worth clinical application.

Keywords: Prostate cancer, bone metastases, predictive model, neutrophil lymphocyte ratio, platelet lymphocyte ratio, lymphocyte/monocyte ratio, albumin/globulin ratio

Introduction

As the second most common malignant tumor worldwide, prostate cancer (PCa) causes more than 1 million new cases and more than 300,000 deaths annually, bringing about great harm to men's health [1, 2]. The incidence of PCa in China is lower than that in European and American countries, but it is rising rapidly [3, 4]. As clinical research [5-7] reveals, the rate of bone metastasis is high in PCa as patients have advanced to the late stage at diagnosis. Bone metastasis can cause a series of bone-related events, including spinal cord compression, pathological fracture and hypercalcemia, which affect the quality of life and long-term survival of patients. Metastatic castration-resistant PCa caused by bone metastasis is also one of the main causes of death in patients with PCa. Currently, many predictive models have been established for bone metastases in PCa patients based on imaging evidence and cytomics and genomics results, offering certain guidance for the individualized management of PCa patients [8-10]. The inflammatory reaction is an injury response of the body to endogenous or exogenous injury. Tumor-related inflammatory reaction plays an important role in tumor initiation, progression and metastasis, and inflammatory markers have great application potential in tumor diagnosis, disease assessment and prognosis assessment [11, 12]. As studies [13-15] reveal, multiple inflammatory factors, including neutrophils, C-reactive protein, lymphocytes, interleukin family and tumor necrosis factor family, can affect the biological behav-

iors of tumor tissues through various channels. Therefore, an inflammatory factor model based on serology detection may have certain clinical value for predicting bone metastasis in PCa patients. Besides, clinical studies [16, 17] have found that composite inflammation indexes, including systemic immune and multiple inflammation indexes, also show clinical value in evaluating various malignant tumors. There is still a lack of application of the composite inflammation indexes for predicting the occurrence of bone metastases in PCa patients. A bone metastasis prediction model based on relatively readily available inflammatory markers is particularly important for early detection and diagnosis of PCa bone metastasis for individualized treatment options, prognosis, and reduction of complications. This issue was discussed in the present study to provide references for the prediction of bone metastasis in patients with PCa.

Data and methods

Research data

In this retrospective study, 162 PCa patients admitted to the Urology Surgery, Shaanxi Provincial People's Hospital from March 2015 to March 2022 were selected as the research subjects. Inclusion criteria: (1) patients who were confirmed with PCa by aspiration biopsy or surgery; (2) patients who received bone SPECT imaging and serological examination within one week before treatment; (3) patients with complete relevant clinical data. Exclusion criteria: (1) patients with a history of prostate surgery or endocrine therapy before admission; (2) patients combined with other malignant tumors or congenital bone diseases; (3) patients with bone metastases that could not be identified; (4) patients complicated with hematological diseases or infectious diseases. Following a random method, 40 of the 162 PCa patients who met the inclusion criteria were included in a validation group (n=40), and the rest in a modeling group (n=122). The patients in the modeling group were divided into a metastatic group (n=67) and a non-metastatic group (n=55) according to the whole-body bone imaging results. All the patients were followed up at 3-month intervals after treatment. The study design was based on the Helsinki Declaration and approved by the Medical Ethics Committee of Urology Surgery, Shaanxi Provincial People's Hospital.

Data collection

Basic information of patients, initial laboratory results and treatment status were obtained from the electronic medical record system. The data including age, clinical stage, Gleason score, hematuria, treatment, androgen deprivation therapy, total prostate specific antigen (tPSA) detection, etc. Laboratory data were collected if no bone metastasis occurred prior to treatment. Inflammatory indicators included neutrophil-lymphocyte ratio (NLR), platelet lymphocyte ratio (PLR), lymphocyte/monocyte ratio (LMR) and albumin/globulin ratio (AGR). All indicators were tested in the laboratory department of our hospital, and all instruments and reagents were from the same manufacturer. The tissue samples obtained by aspiration biopsy or surgical sampling from patients were prepared as pathological sections and stained with H&E. Two experienced pathologists completed the Gleason score assessment. According to the assessment results, the scores were given, including 2-4 as highly differentiated, 5-7 as moderately differentiated, and 8-10 as lowly differentiated or undifferentiated.

Statistical analysis

SPSS 23.0 was used to analyze the collected experimental data. The measurement data following normal distribution were represented by mean ± standard deviation ($X \pm S$), and the independent sample t-test was used for their comparison. The counting data were expressed as cases or rates, and the χ^2 test was used for the comparison. The logistics regression model was used to estimate the odds ratio (OR) of each candidate variable, and variables with $P< 0.05$ in univariate analysis were included in multivariate analysis. The predictive model was established based on the coefficient β in the multivariate regression results. The receiver operating characteristic (ROC) curve was used to evaluate the prediction efficiency of the model for bone metastasis in the modeling and validation groups. Graphpad 8.0 software was used for plotting. DeLong method was used for pairwise comparison of ROC curve results. The calibration curve, discrimination degree and C-index were used to comprehensively evaluate the model's performance. All statistical tests were two-sided, and $P<0.05$ was considered statistically significant.

Table 1. Comparison of clinical data between modeling group and validation group

Factor		Validation group (n=40)	Modeling group (n=122)	t/χ^2	*P*
Age (years)		69.85±10.76	70.15±11.83	0.142	0.887
Clinical stage (T1-T2/T3-T4)		8/32	22/90	0.002	0.961
Total Gleason score (points)		7.90±2.11	7.99±1.72	0.271	0.787
Hematuria (cases)		16	49	0.001	0.985
Therapeutic method	Bisphosphate	19	62	0.445	0.931
	Docetaxel	13	33		
	Abiraterone	3	10		
	Untreated	5	17		
Androgen deprivation therapy	Persistent	26	71	0.580	0.446
	Intermittent	14	51		
tPSA (ng/mL)		108.63±43.97	116.35±45.67	0.936	0.351
NLR		2.59±0.56	2.64±0.59	0.471	0.638
PLR		110.85±31.67	113.86±33.49	0.500	0.618
LMR		3.54±0.71	3.49±0.69	0.395	0.693
AGR		0.88±0.23	0.91±0.21	0.766	0.445

Note: tPSA: total Prostate Specific Antigen; NLR: Neutrophil-Lymphocyte Ratio; PLR: Platelet Lymphocyte Ratio; LMR: Lymphocyte/Monocyte Ratio; AGR: Albumin/Globulin Ratio.

Results

Comparison of clinical data between the modeling group and the validation group

There were no significant differences in age, clinical stage, total Gleason score, hematuria, treatment methods, androgen deprivation therapy, tPSA, PASD, NLR, PLR, LMR and AGR between the modeling group and the validation group (all P>0.05, **Table 1**).

Comparison of clinical data between the metastatic group and the non-metastatic group

No significant differences were observed in sex, clinical stage, hematuria, treatment methods and androgen deprivation therapy between the two groups (all P>0.05). The total Gleason score and AGR in the metastatic group were lower than those in the non-metastatic group, and the tPSA, NLR, PLR and LMR in the metastatic group were higher than those in the non-metastatic group, with significant differences (all P<0.05, **Table 2**).

Multivariate Logistics regression analysis of influencing factors for bone metastasis in PCa

The metastasis was taken as the dependent variable (yes =1, no =0), and the total Gleason score, tPSA, NLR, PLR, LMR and AGR (all substituted with actual values) were taken as the independent variables for multivariate analysis. The results of Logistics regression analysis showed that, total Gleason score, tPSA, NLR, PLR, LMR and AGR were independent influencing factors of bone metastasis in PCa patients (all P<0.05, **Table 3**).

Establishment and performance evaluation of the predictive model

The predictive model was established according to the results of Logistics regression analysis: Logit (P) = -5.341 + 0.930*total Gleason score + 1.426*tPSA + 0.836*NLR + 0.896*PLR + 0.641*LMR + 0.750*AGR. Based on this equation, the regression model was constructed for ROC analysis. The ROC analysis showed that the areas under the curve of the predictive model for bone metastasis in the modeling and validation groups were 0.896 and 0.870, respectively. The standard errors were 0.029 and 0.033, and the 95% CI were 0.840-0.952 and 0.805-0.936, respectively (**Figures 1**, **2**). There was no significant difference between the two groups (Z=1.818, P=0.535).

Evaluation of the predictive model

The Hosmer-Lemeshow test was used to test the fitting degree of this model. The results showed that P=0.253, indicating that the information in the current data had been fully extracted, and the degree of fitting was high. The internal verification results showed that the C-index of the predictive model established in

Table 2. Comparison of clinical data between metastatic group and non-metastatic group

Factor		Metastatic (n=67)	Non-metastatic group (n=55)	t/χ^2	*P*
Age (years)		70.27±12.12	70.00±11.69	0.124	0.901
Clinical stage (T1-T2/T3-T4)		12/55	10/45	0.001	0.969
Total Gleason score (points)		7.54±1.39	8.55±1.95	3.333	0.001
Hematuria (cases)		26	23	0.114	0.736
Therapeutic method	Bisphosphonate	32	30	1.613	0.656
	Docetaxel	15	10		
	Abiraterone	6	7		
	Untreated	14	8		
Androgen deprivation therapy	Persistent	41	30	0.549	0.459
	Intermittent	26	25		
tPSA (ng/mL)		128.02±36.63	105.86±35.76	3.361	0.001
NLR		2.83±0.55	2.39±0.55	4.397	<0.001
PLR		127.89±29.28	96.78±30.73	5.710	<0.001
LMR		3.80±0.54	3.07±0.59	7.125	<0.001
AGR		0.84±0.20	1.01±0.21	4.567	<0.001

Note: tPSA: total Prostate Specific Antigen; NLR: Neutrophil-Lymphocyte Ratio; PLR: Platelet Lymphocyte Ratio; LMR: Lymphocyte/Monocyte Ratio; AGR: Albumin/Globulin Ratio.

Table 3. Multivariate Logistics regression analysis of influencing factors of bone metastasis in PCa

Risk factor	B-value	SE-value	Ward-value	Adjust OR-value	95% CI	*P*-value
Total Gleason score	0.930	0.241	14.897	2.535	1.581-4.056	<0.001
tPSA	1.426	0.331	18.566	4.163	2.176-7.965	<0.001
NLR	0.836	0.222	14.164	2.306	1.492-3.563	<0.001
PLR	0.896	0.231	15.034	2.449	1.557-3.851	<0.001
LMR	0.641	0.211	9.238	1.899	1.256-2.872	<0.001
AGR	0.750	0.220	11.637	2.118	1.376-3.260	<0.001

Note: PCa: Prostate Cancer; tPSA: total Prostate Specific Antigen; NLR: Neutrophil-Lymphocyte Ratio; PLR: Platelet Lymphocyte Ratio; LMR: Lymphocyte/Monocyte Ratio; AGR: Albumin/Globulin Ratio.

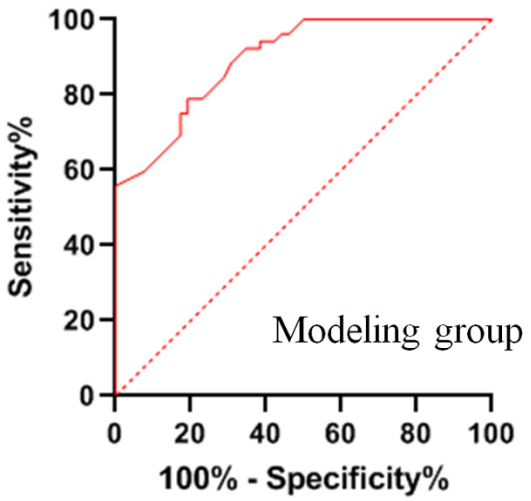

Figure 1. Performance of the predictive model for bone metastasis in prostate cancer in the modeling group.

this study was 0.760 (95% CI: 0.670-0.851) for predicting bone metastasis of PCa, indicating that the model was in good agreement with the actual occurrence of metastasis.

Discussion

The diagnosis of bone metastasis of PCa is of great significance for the treatment and prognosis. For, early diagnosis of bone metastasis, bone scan is the most used method, but the diagnostic specificity of bone scan is low, and there is a high false positive. In recent years, with computed tomography, magnetic resonance imaging, emission computer tomography, positron emission computed tomography, and deep learning algorithms-convolutional neural networks, the diagnosis methods for bone metastasis were further studied. A variety of auxiliary parameters are also used in the

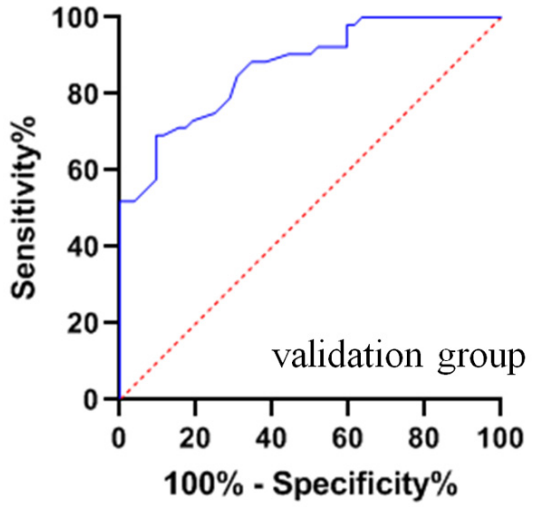

Figure 2. Performance of the predictive model for bone metastasis in the validation group.

diagnosis of bone metastasis, significantly improving the accuracy of the diagnosis of bone metastasis. To evaluate and improve the therapeutic effect of patients with PCa bone metastases, treatment for bone metastases is expected while diagnosing.

According to studies [18, 19], 41.9% of PCa patients have complications such as spinal cord compression and pathological fractures within 2 years after diagnosis of bone metastases, which dramatically impact the quality of life of patients and causes a tremendous economic burden. Therefore, reducing or delaying the occurrence of related complications is of great significance for improving the long-term prognosis of patients [20, 21]. Tumor microenvironment is an essential factor affecting the prognosis of PCa patients, and inflammatory reaction plays a vital role in the progression and metastasis of malignant tumors [22].

The inflammatory response is an anti-injury response of the body to endogenous or exogenous damage. Tumor-related inflammation plays an important role in the occurrence, development, malignant transformation, invasion and metastasis of tumors and affects the host's anti-tumor immunity. The persistent systemic inflammation and the inflammatory response of the tumor itself stimulate the body to produce many inflammatory cells. Neutrophils and lymphocytes can enhance the adhesion of tumor cells to distant metastasis by secreting soluble factors and further activating endothelial cells and parenchymal cells. Lymphocytes are crucial in cancer immune monitoring. Platelets also play an essential role in inflammation and tumor biology. Many vascular endothelial growth factors in platelets can directly act on tumor cells, and promote tumor growth, invasion and angiogenesis. Platelets adhere to the surface of circulating tumor cells to form platelet coatings, thereby reducing the damage of free tumor cells by blood flow shear stress and immune attack. However, the efficacy of single inflammatory index for tumor prognosis assessment is often insufficient, and combining multiple inflammatory indicators has significant benefits to improving the application efficacy. The results of this study showed that in the metastatic group, the total Gleason score and AGR were lower than those in the non-metastatic group, while the tPSA, NLR, PLR and LMR were higher than those in the non-metastatic group. Logistics regression analysis showed that the total Gleason score, tPSA, NLR, PLR, LMR and AGR were independent influencing factors for bone metastasis in PCa patients. It was confirmed that NLR, PLR, LMR and AGR might be involved in the process of bone metastasis. Previous studies [23, 24] have found that NLR, PLR, MLR and AGR are closely related to the prognosis of PCa patients. In addition, albumin, produced in the liver and accounts for about 50% of plasma proteins, regulates blood colloid osmotic pressure and maintains the whole blood volume. Globulin, including immunoglobulin, antibody and glycoprotein, is the most crucial protein substance in the blood, which is involved in blood coagulation, protein transport and antibody level regulation. AGR level changes are closely related to various chronic inflammatory diseases and tumor progression [25, 26].

In this study, a predictive model was established based on the results of Logistics regression analysis. ROC analysis, Hosmer-Lemeshow test and externality test were successively used to evaluate the model's prediction performance, degree of fitting and consistency. The results showed that the model had a good predictive performance for bone metastasis in PCa patients in both modeling and validation groups. Hosmer-Lemeshow and externality tests also proved that the model had good fitting and consistency. Compared with the previ-

ous simple analysis of the impact of single factors on clinical outcomes, Logistics regression analysis can provide better visibility and better quantitative reflection on the impact of indicators on outcomes. It has been proven in several studies that modeling is better than single-indicator prediction [27, 28].

There are some shortcomings in this study. For example, this study is a single-center retrospective study. Since the quality of medical records cannot be controlled, there might be some bias in the research conclusion. Besides, the level of inflammatory markers are affected by tumor, comorbidities and therapeutic drugs. The deficiencies of this study are that, first of all, this study is a single-center study, the number of cases included is relatively small, which may cause some inadequate information; secondly, due to the limitations of medical records, some valuable variables may not be included in the statistics; thirdly, the prediction model established in this study was based on the cohort of PCa patients in our hospital and was not validated in other hospitals. Therefore, in future studies, the sample size and the number of research institutions need to be further expanded to improve and supplement the conclusions. The results of this study proved that the predictive model for bone metastasis in PCa patients based on multiple immune inflammatory parameters (NLR, PLR, LMR and AGR) could better predict the occurrence of bone metastasis in PCa patients. In our review, this model is worth of clinical application, especially in primary hospitals, as it can provide references and ideas for individualized treatment in PCa patients.

Acknowledgements

Supported by Shaanxi Natural Science Basic Research Program “Research of the invasion and metastasis mechanism mediated by LncRNA MEG3/miR-181/GATA6 axis in prostate cancer cells” (No.2023-JC-YB-796).

Disclosure of conflict of interest

None.

Address correspondence to: Qingchuan Dong, Urology Surgery, Shaanxi Provincial People’s Hospital, Xi’an 710068, Shaanxi, China. Tel: +86-029-85251-331; E-mail: dongqc169@163.com

References

[1] Hofman MS, Lawrentschuk N, Francis RJ, Tang C, Vela I, Thomas P, Rutherford N, Martin JM, Frydenberg M, Shakher R, Wong LM, Taubman K, Ting Lee S, Hsiao E, Roach P, Nottage M, Kirkwood I, Hayne D, Link E, Marusic P, Matera A, Herschtal A, Iravani A, Hicks RJ, Williams S and Murphy DG; proPSMA Study Group Collaborators. Prostate-specific membrane antigen PET-CT in patients with high-risk prostate cancer before curative-intent surgery or radiotherapy (proPSMA): a prospective, randomised, multicentre study. Lancet 2020; 395: 1208-1216.

[2] Fornetti J, Welm AL and Stewart SA. Understanding the bone in cancer metastasis. J Bone Miner Res 2018; 33: 2099-2113.

[3] Logothetis C, Morris MJ, Den R and Coleman RE. Current perspectives on bone metastases in castrate-resistant prostate cancer. Cancer Metastasis Rev 2018; 37: 189-196.

[4] Kyriakopoulos CE, Chen YH, Carducci MA, Liu G, Jarrard DF, Hahn NM, Shevrin DH, Dreicer R, Hussain M, Eisenberger M, Kohli M, Plimack ER, Vogelzang NJ, Picus J, Cooney MM, Garcia JA, DiPaola RS and Sweeney CJ. Chemohormonal therapy in metastatic hormone-sensitive prostate cancer: long-term survival analysis of the randomized phase III E3805 CHAARTED trial. J Clin Oncol 2018; 36: 1080-1087.

[5] Gillessen S, Attard G, Beer TM, Beltran H, Bjartell A, Bossi A, Briganti A, Bristow RG, Chi KN, Clarke N, Davis ID, de Bono J, Drake CG, Duran I, Eeles R, Efstathiou E, Evans CP, Fanti S, Feng FY, Fizazi K, Frydenberg M, Gleave M, Halabi S, Heidenreich A, Heinrich D, Higano CTS, Hofman MS, Hussain M, James N, Kanesvaran R, Kantoff P, Khauli RB, Leibowitz R, Logothetis C, Maluf F, Millman R, Morgans AK, Morris MJ, Mottet N, Mrabti H, Murphy DG, Murthy V, Oh WK, Ost P, O’Sullivan JM, Padhani AR, Parker C, Poon DMC, Pritchard CC, Reiter RE, Roach M, Rubin M, Ryan CJ, Saad F, Sade JP, Sartor O, Scher HI, Shore N, Small E, Smith M, Soule H, Sternberg CN, Steuber T, Suzuki H, Sweeney C, Sydes MR, Taplin ME, Tombal B, Türkeri L, van Oort I, Zapatero A and Omlin A. Management of patients with advanced prostate cancer: report of the advanced prostate cancer consensus conference 2019. Eur Urol 2020; 77: 508-547.

[6] Rogowski P, Roach M 3rd, Schmidt-Hegemann NS, Trapp C, von Bestenbostel R, Shi R, Buchner A, Stief C, Belka C and Li M. Radiotherapy of oligometastatic prostate cancer: a systematic review. Radiat Oncol 2021; 16: 50.

[7] Zhang J, Zhai G, Yang B and Liu Z. Computerized tomography (CT) updates and challenges in diagnosis of bone metastases during prostate cancer. Curr Med Imaging 2020; 16: 565-571.
[8] Li L, Ameri AH, Wang S, Jansson KH, Casey OM, Yang Q, Beshiri ML, Fang L, Lake RG, Agarwal S, Alilin AN, Xu W, Yin J and Kelly K. EGR1 regulates angiogenic and osteoclastogenic factors in prostate cancer and promotes metastasis. Oncogene 2019; 38: 6241-6255.
[9] Ottosson F, Baco E, Lauritzen PM and Rud E. The prevalence and locations of bone metastases using whole-body MRI in treatment-naïve intermediate- and high-risk prostate cancer. Eur Radiol 2021; 31: 2747-2753.
[10] Violet J, Jackson P, Ferdinandus J, Sandhu S, Akhurst T, Iravani A, Kong G, Kumar AR, Thang SP, Eu P, Scalzo M, Murphy D, Williams S, Hicks RJ and Hofman MS. Dosimetry of 177Lu-PSMA-617 in metastatic castration-resistant prostate cancer: correlations between pretherapeutic imaging and whole-body tumor dosimetry with treatment outcomes. J Nucl Med 2019; 60: 517-523.
[11] Zhang JY, Ge P, Zhang PY, Zhao M and Ren L. Role of neutrophil to lymphocyte ratio or platelet to lymphocyte ratio in prediction of bone metastasis of prostate cancer. Clin Lab 2019; 65: 1-10.
[12] Bauckneht M, Rebuzzi SE, Signori A, Frantellizzi V, Murianni V, Lodi Rizzini E, Mascia M, Lavelli V, Donegani MI, Ponzano M, Gaudiano A, Stazza ML, Licari M, Cavallini L, Laghi V, Cindolo L, Maggi M, Sciarra A, Mammucci P, Sambuceti G, Costa RP, Spanu A, Rubini G, Monari F, De Vincentis G and Fornarini G. The prognostic power of inflammatory indices and clinical factors in metastatic castration-resistant prostate cancer patients treated with radium-223 (BIO-Ra study). Eur J Nucl Med Mol Imaging 2022; 49: 1063-1074.
[13] Nakanishi K, Tanaka J, Nakaya Y, Maeda N, Sakamoto A, Nakayama A, Satomura H, Sakai M, Konishi K, Yamamoto Y, Nagahara A, Nishimura K, Takenaka S and Tomiyama N. Whole-body MRI: detecting bone metastases from prostate cancer. Jpn J Radiol 2022; 40: 229-244.
[14] Ali A, Hoyle A, Haran ÁM, Brawley CD, Cook A, Amos C, Calvert J, Douis H, Mason MD, Dearnaley D, Attard G, Gillessen S, Parmar MKB, Parker CC, Sydes MR, James ND and Clarke NW. Association of bone metastatic burden with survival benefit from prostate radiotherapy in patients with newly diagnosed metastatic prostate cancer: a secondary analysis of a randomized clinical trial. JAMA Oncol 2021; 7: 555-563.
[15] Conteduca V, Oromendia C, Eng KW, Bareja R, Sigouros M, Molina A, Faltas BM, Sboner A, Mosquera JM, Elemento O, Nanus DM, Tagawa ST, Ballman KV and Beltran H. Clinical features of neuroendocrine prostate cancer. Eur J Cancer 2019; 121: 7-18.
[16] Hiraga T. Bone metastasis: interaction between cancer cells and bone microenvironment. J Oral Biosci 2019; 61: 95-98.
[17] Buckup M, Rice MA, Hsu EC, Garcia-Marques F, Liu S, Aslan M, Bermudez A, Huang J, Pitteri SJ and Stoyanova T. Plectin is a regulator of prostate cancer growth and metastasis. Oncogene 2021; 40: 663-676.
[18] Zhou T, Zhou F, Guo J, Shi H, Yao X, Guo H, Yuan J, Tian Y, Zhang X, Wang S, Jiang Y, Zou Q, Zhou D, Li H, Li F, Lee JL, Chen CH, Park SH, Ng QS, Ma J, Zheng R, Ding Q, Liu X, Li R, Krissel H, Wagner VJ and Sun Y. Radium-223 in Asian patients with castration-resistant prostate cancer with symptomatic bone metastases: a single-arm phase 3 study. Asia Pac J Clin Oncol 2021; 17: 462-470.
[19] Chao YL, Chao M, Xiang RY, Ying JH, Gang Z, Yun HR and Yu G. Risk factors of bone metastasis in patients with newly diagnosed prostate cancer. Eur Rev Med Pharmacol Sci 2022; 26: 391-398.
[20] Belmonte M, Saia G, Zugni F, Alessi S, Colombo A, Summers PE, Luzzago S, Marvaso G, Musi G, De Cobelli O, Jereczek-Fossa BA and Petralia G. The role of MRI in the management of a prostate cancer patient with bone and lymph nodes metastases. A case report. Acta Biomed 2021; 92: e2021214.
[21] Clemons M, Liu M, Stober C, Pond G, Jemaan Alzahrani M, Ong M, Ernst S, Booth C, Mates M, Abraham Joy A, Aseyev O, Blanchette P, Vandermeer L, Tu M, Thavorn K and Fergusson D; REaCT Investigators. Two-year results of a randomised trial comparing 4- versus 12-weekly bone-targeted agent use in patients with bone metastases from breast or castration-resistant prostate cancer. J Bone Oncol 2021; 30: 100388.
[22] Wang Y, Wu N and Jiang N. Autophagy provides a conceptual therapeutic framework for bone metastasis from prostate cancer. Cell Death Dis 2021; 12: 909.
[23] Turker S, Cilbir E, Guven DC, Karacin C and Yalcin S. The relation between inflammation-based parameters and survival in metastatic pancreatic cancer. J Cancer Res Ther 2021; 17: 510-515.
[24] Solanki SL, Kaur J, Gupta AM, Patkar S, Joshi R, Ambulkar RP, Patil A and Goel M. Cancer related nutritional and inflammatory markers as predictive parameters of immediate postoperative complications and long-term survival af-

ter hepatectomies. Surg Oncol 2021; 37: 101526.
[25] Zhang W, Yang F, Kadier A, Chen Y, Yu Y, Zhang J, Geng J, Yan Y, Li W and Yao X. Development of nomograms related to inflammatory biomarkers to estimate the prognosis of bladder cancer after radical cystectomy. Ann Transl Med 2021; 9: 1440.
[26] Zhang W, Yang F, Kadier A, Chen Y, Yu Y, Zhang J, Geng J, Yan Y, Li W and Yao X. Development of nomograms related to inflammatory biomarkers to estimate the prognosis of bladder cancer after radical cystectomy. Ann Transl Med 2021; 9: 1440.
[27] Li XY, You JX, Zhang LY, Su LX and Yang XT. A novel model based on necroptosis-related genes for predicting prognosis of patients with prostate adenocarcinoma. Front Bioeng Biotechnol 2022; 9: 814813.
[28] Sakaguchi K, Hayashida M, Tanaka N, Oka S and Urakami S. A risk model for detecting clinically significant prostate cancer based on biparametric magnetic resonance imaging in a Japanese cohort. Sci Rep 2021; 11: 18829.