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ORIGINAL RESEARCH

Geriatric Nutritional Risk Index (GNRI) and Prognostic Nutritional Index (PNI) Before Treatment as the Predictive Indicators for Bone Metastasis in Prostate Cancer Patients

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Objective: Inflammation and nutritional status are involved in the occurrence and progression of cancer. The purpose of this study was to investigate the relationship of nutritional status indices (geriatric nutritional risk index (GNRI), neutrophil to albumin ratio (NAR), prognostic nutritional index (PNI)), and comprehensive inflammatory indices (pan-immune inflammation value (PIV), systemic immune inflammation index (SII), and system inflammation response index (SIRI)) and bone metastasis of prostate cancer.
Methods: A retrospective analysis was performed on 888 prostate cancer patients treated in Meizhou People's Hospital from November 2017 to December 2022. Clinical characteristics were collected, including age, body mass index (BMI), bone metastasis, and GNRI, NAR, PNI, PIV, SII, and SIRI levels. The optimal cutoff values of these indices were calculated by receiver operating characteristic (ROC) curve, and the relationship between these indices and bone metastasis was analyzed.
Results: There were 836 (94.1%) cases were ≥60 years old, indicating that the majority of prostate cancer patients were elderly men. There were 640 (72.1%) patients without bone metastasis and 248 (27.9%) patients with bone metastasis. The levels of GNRI and PNI in patients with bone metastasis were significantly lower than those without, while NAR, PIV, SII, and SIRI were not statistically significant. And the levels of GNRI and PNI in patients with multiple bone metastasis were significantly lower than those with single bone metastasis. When bone metastasis was taken as the endpoint of GNRI and PNI, the critical value of GNRI was 97.05 (sensitivity 55.2%, specificity 67.5%, area under the ROC curve (AUC) = 0.639), the PNI cutoff value was 44.925 (sensitivity 51.2%, specificity 67.2%, AUC = 0.634), and the AUC of GNRI plus PNI was 0.647.
Conclusion: Prostate cancer is more common in older men; about a quarter of patients have bone metastasis. GNRI and PNI have predictive efficacy in bone metastasis and multiple bone metastasis of prostate cancer, but NAR, PIV, SII, and SIRI do not.
Keywords: prostate cancer, bone metastasis, geriatric nutritional risk index, prognostic nutritional index

Introduction

Prostate cancer is an epithelial malignant tumor occurring in the prostate and is the most common malignant tumor of the male genitourinary system.[1] Prostate cancer has become the second most common cancer in men worldwide after lung cancer.[2] Both the incidence and mortality of prostate cancer are on the rise in China.[3–5] With the intensification of global population aging, the incidence of prostate cancer will increase.[6] The onset of prostate cancer is occultic, and most of the patients have no obvious symptoms in the early stage, and some of them are already in the advanced stage when they are found.[7] In some patients, tumor metastasis is found at first visit, leading to a decrease in quality of life.[8]

For the treatment of prostate cancer, radical treatment has a relatively high effectiveness and focal therapy has fewer side effects.[9] Tumor metastasis is a thorny issue that has to be faced in the treatment of prostate cancer. Approximately 54% of patients have distant metastases at the time of initial diagnosis, among which about 80% are bone metastasis.[10] Bone metastasis of prostate cancer often cause skeletal related events (SREs) and a series of other complications, which are the main causes of quality of life decline and death in patients with metastatic prostate cancer.[11] SREs caused by bone metastasis of prostate cancer include pathological fracture, spinal cord compression, bone surgery, and bone radiation therapy.[12] Effective prediction of the risk of bone metastasis in prostate cancer patients is beneficial to the treatment and prognosis of patients. Magnetic resonance imaging (MRI) has high sensitivity and specificity in the diagnosis of bone metastases in prostate cancer, but it is limited in the diagnosis of long limbs and cortical metastases.[13] Positron emission computed tomography (PET) can find smaller and more bone marrow lesions, but the detection is time-consuming and the patient tolerance is poor, and the clinical application value needs to be further analyzed.[14] Bone biopsy usually produces less tumor tissue, and it is difficult to carry out widely as an invasive examination.[15] The detection of peripheral blood markers has potential value in the prediction of bone metastasis of prostate cancer due to its convenient specimen acquisition and simple detection method.

Inflammation and nutritional status are involved in the occurrence and development of some diseases[16,17] and are now receiving extensive attention.[18] Nutritional deficiency can disrupt the regulation of prostate hormones, induce oxidative stress and inflammation, alter growth factor signaling and lipid metabolism, and promote the occurrence and progression of prostate cancer.[19] At present, some comprehensive indices based on serum albumin levels have gradually gained recognition in the assessment of disease progression and prognosis. Geriatric nutritional risk index (GNRI), which is used to assess an individual's nutritional status, has been shown to be associated with a number of diseases and is considered a potentially valuable indicator in tumors.[20,21] Neutrophil to albumin ratio (NAR) is an important index that comprehensively reflects the level of systemic immunity and nutritional status and has been proved to be closely related to tumor and cardiovascular and cerebrovascular diseases by many studies.[22,23] Prognostic nutritional index (PNI) which can reflect the immune and nutritional status of the host and serve as an effective prognostic factor for a variety of tumors.[24,25]

The occurrence and development of many human diseases are more or less involved in the process of immune inflammatory response.[26,27] Immunoinflammatory response is also involved in the development and progression of tumors.[28,29] The tumor microenvironment (TME) is an important site for the growth, proliferation, and metastasis of tumor cells, among which the infiltration of inflammatory cells is one of its significant characteristics.[30] The inflammatory response regulates the expression of a series of genes related to cell proliferation, survival, invasion and metastasis, thereby promoting the development of cancer.[31] In addition, inflammation can also support the growth and metastasis of tumors by inducing angiogenesis, providing sufficient nutrition and oxygen to tumor cells.[32] In recent years, some comprehensive inflammatory indices (pan-immune inflammation value (PIV), systemic immune inflammation index (SII), and system inflammation response index (SIRI)) have received widespread attention. SII is a comprehensive index of neutrophils, platelets and lymphocytes, and has been proven to predict the prognosis of liver cancer, pancreatic cancer, cervical cancer and other cancers.[33,34] The SIRI index, an indicator of overall lymphocytes, monocytes, and neutrophils levels, has been linked to the prognosis of pancreatic, gastric, and breast cancers.[35–37] However, the predictive value of GNRI, NAR, PNI, PIV, SII, and SIRI in prostate cancer bone metastasis is unclear. This study evaluated the relationship between these indicators and bone metastasis in patients with prostate cancer.

Materials and Methods
Subjects

The prostate cancer patients, who were hospitalized in Meizhou People's Hospital from November 2017 to December 2022, were included in this study. Inclusion criteria: (1) prostate cancer patients were confirmed by histopathology examination; (2) whole-body bone scans are performed using emission computed tomography (ECT), computed tomography (CT), magnetic resonance imaging (MRI), or nuclide bone imaging; (3) medical records were complete; and (4) serum albumin, and peripheral blood cell analysis was performed at least once before surgery, and there were no inflammation-related factors affecting blood indexes. Exclusion criteria: (1) patients with other malignant tumor diseases; (2) patients with diseases that affect relevant peripheral blood

inflammatory indicators, such as severe infections, autoimmune diseases, and so on; (3) patients with dysfunction of important organs; and (4) medical records were incomplete. The study was approved by the Ethics Committee of Medicine, Meizhou People's Hospital (Clearance No.: 2024-C-241).

Data Collection

Clinical characteristics of the patients were collected from the medical records system of our hospital, including age, body mass index (BMI), and bone metastasis. Blood routine test data were collected at admission and before treatment. The blood cell analysis was tested by the Sysmex XE-2100 haematology analyzer (Sysmex Corporation, Japan) and serum albumin was measured by Roche automatic biochemical analyzer, according to standard operating procedures (SOP).

Data Processing and Statistical Analysis

The inflammation index GNRI, NAR, PNI, PIV, SII, and SIRI were calculated according to the following formula:

$$GNRI = 1.489 \times serum\,albumin\,(g/L) + 41.7 \times actual\,body\,weight\,(kg)/ideal\,body\,weight\,(kg)$$

$$NAR = neutrophil\,count/serum\,albumin$$

$$PNI = serum\,albumin\,(g/L) + 5 \times lymphocyte\,count$$

$$PIV = monocyte \times neutrophil \times platelet/lymphocyte$$

$$SII = platelet \times neutrophil/lymphocyte$$

$$SIRI = monocyte \times neutrophil/lymphocyte$$

SPSS statistical software version 26.0 (IBM Inc., USA) and GraphPad Prism 8.0 were used for data analysis and mapping, and continuous data were compared using t-test or Mann–Whitney U-test. The categorical variables were compared using by Chi-square test or Fisher's exact test. Receiver operating characteristic (ROC) curve analysis was used to determine the optimal cutoff values of GNRI, NAR, PNI, PIV, SII, and SIRI to distinguish bone metastasis of prostate cancer. $p<0.05$ was set as statistically significant.

Results
Clinical Characteristics of Prostate Cancer Patients

There were 888 patients with prostate cancer, 52 (5.9%) cases were <60 years old and 836 (94.1%) cases were ≥60 years old, indicating that the majority of prostate cancer patients were elderly men. There were 94 (10.6%) cases with BMI <18.5 kg/m^2, 515 (58.0%) cases with BMI 18.5–23.9 kg/m^2, and 279 (31.4%) cases with BMI ≥24.0 kg/m^2 (Table 1).

In this study, there were 640 (640/888, 72.1%) patients without bone metastasis and 248 (248/888, 27.9%) patients with bone metastasis. The levels of albumin and lymphocyte count in bone metastasis group were lower than those in non-bone metastasis group ($p<0.001$). The differences of levels of neutrophil count, monocytes count, and platelet count were not statistically significant between the two groups (Table 1).

Comparison of GNRI, NAR, PNI, PIV, SII, and SIRI in Prostate Cancer Patients with or without Bone Metastasis

The levels of GNRI (96.15 (88.38, 103.15) vs 100.90 (94.80, 107.30), $p<0.001$) and PNI (44.80 (40.36, 48.88) vs 47.55 (43.75, 51.60), $p<0.001$) in patients with bone metastasis were significantly lower than those in patients without bone metastasis. The differences of levels of NAR, PIV, SII, and SIRI were not statistically significant between patients with and without bone metastasis (Figure 1).

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Table 1 Characteristics and Laboratory Parameters of Prostate Cancer Patients with and without Bone Metastasis

Clinical Characteristics	Prostate Cancer Patients (n=888)	Non-Bone Metastasis Group (n=640)	Bone Metastasis Group (n=248)	χ^2/Z	P values
Age (Years)					
<60, n (%)	52 (5.9%)	41 (6.4%)	11 (4.4%)	χ^2=1.259	0.272
≥60, n (%)	836 (94.1%)	599 (93.6%)	237 (95.6%)		
BMI (kg/m^2)					
<18.5	94 (10.6%)	52 (8.1%)	42 (16.9%)	χ^2=18.217	<0.001
18.5–23.9	515 (58.0%)	370 (57.8%)	145 (58.5%)		
≥24.0	279 (31.4%)	218 (34.1%)	61 (24.6%)		
Serum albumin (g/L), median (P25, P75)	38.80 (35.80, 41.78)	39.35 (36.50, 42.20)	36.95 (34.13, 40.38)	Z=−5.925	<0.001
Lymphocyte (×10^9/L), median (P25, P75)	1.57 (1.20, 2.00)	1.60 (1.29, 2.00)	1.49 (1.10, 1.89)	Z=−3.702	<0.001
Neutrophil (×10^9/L), median (P25, P75)	4.36 (3.40, 5.80)	4.40 (3.41, 5.70)	4.29 (3.33, 6.07)	Z=−0.204	0.839
Monocytes (×10^9/L), median (P25, P75)	0.50 (0.40, 0.67)	0.50 (0.40, 0.65)	0.50 (0.39, 0.70)	Z=−0.100	0.920
Platelet (×10^9/L), median (P25, P75)	221.0 (175.0, 265.0)	220.0 (177.0, 262.0)	223.5 (166.0, 282.8)	Z=−0.435	0.664

Abbreviations: BMI, body mass index; p25, 25th percentile; p75, 75th percentile.

Comparison of GNRI, NAR, PNI, PIV, SII, and SIRI in Prostate Cancer Patients with Non-Bone Metastasis, Single Bone Metastasis, and Multiple Bone Metastasis

The levels of GNRI (95.00 (87.90, 102.70) vs 100.90 (94.80, 107.30), $p<0.001$) and PNI (44.10 (40.25, 48.35) vs 47.55 (43.75, 51.60), $p<0.001$) in patients with multiple bone metastasis were significantly lower than those in patients without
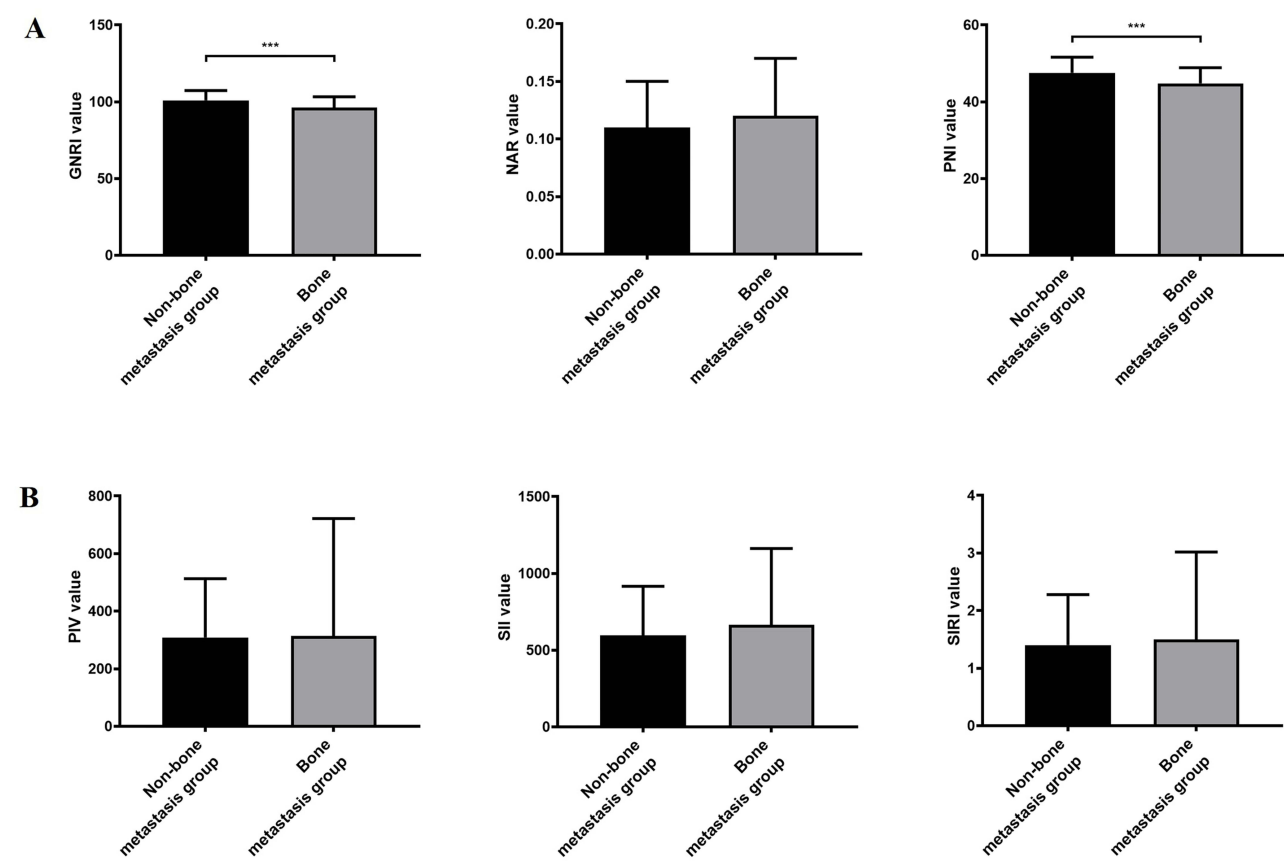

Figure 1 Comparison of nutritional status indices (GNRI, NAR, and PNI) (**A**) and comprehensive inflammatory indices (PIV, SII, and SIRI) (**B**) in prostate cancer patients with or without bone metastasis.
Note: ***$P<0.001$.
Abbreviations: GNRI, geriatric nutritional risk index; NAR, neutrophil to albumin ratio; PNI, prognostic nutritional index; PIV, pan-immune inflammation value; SII, systemic immune inflammation index; SIRI, system inflammation response index.

bone metastasis. The levels of GNRI (95.00 (87.90, 102.70) vs 100.20 (96.00, 106.50), $p<0.001$) and PNI (44.10 (40.25, 48.35) vs 48.50 (45.20, 51.10), $p<0.001$) in patients with multiple bone metastasis were significantly lower than those in patients with single bone metastasis (Figure 2A).

The levels of SII (702.73 (396.84, 1209.59) vs 594.68 (403.49, 916.32), $p=0.042$) and SIRI (1.540 (0.955, 3.100) vs 1.400 (0.883, 2.278), $p=0.020$) in patients with multiple bone metastasis were significantly higher than those in patients without bone metastasis (Figure 2B).

ROC Analysis of GNRI, and PNI Used in the Differential Diagnosis of Bone Metastasis in Prostate Cancer

When bone metastasis was taken as the endpoint of GNRI and PNI, the critical value of GNRI was 97.05 (sensitivity 55.2%, specificity 67.5%, area under the ROC curve (AUC) = 0.639), the PNI cutoff value was 44.925 (sensitivity 51.2%, specificity 67.2%, AUC = 0.634), and the AUC of GNRI plus PNI was 0.647 (Figure 3A).

When multiple bone metastasis was taken as the endpoint (single bone metastasis as control) of GNRI and PNI, the critical value of GNRI was 95.95 (sensitivity 53.1%, specificity 76.9%, AUC = 0.649), the PNI cutoff value was 44.575 (sensitivity 53.6%, specificity 82.1%, AUC = 0.683), and the AUC of GNRI plus PNI was 0.687 (Figure 3B).
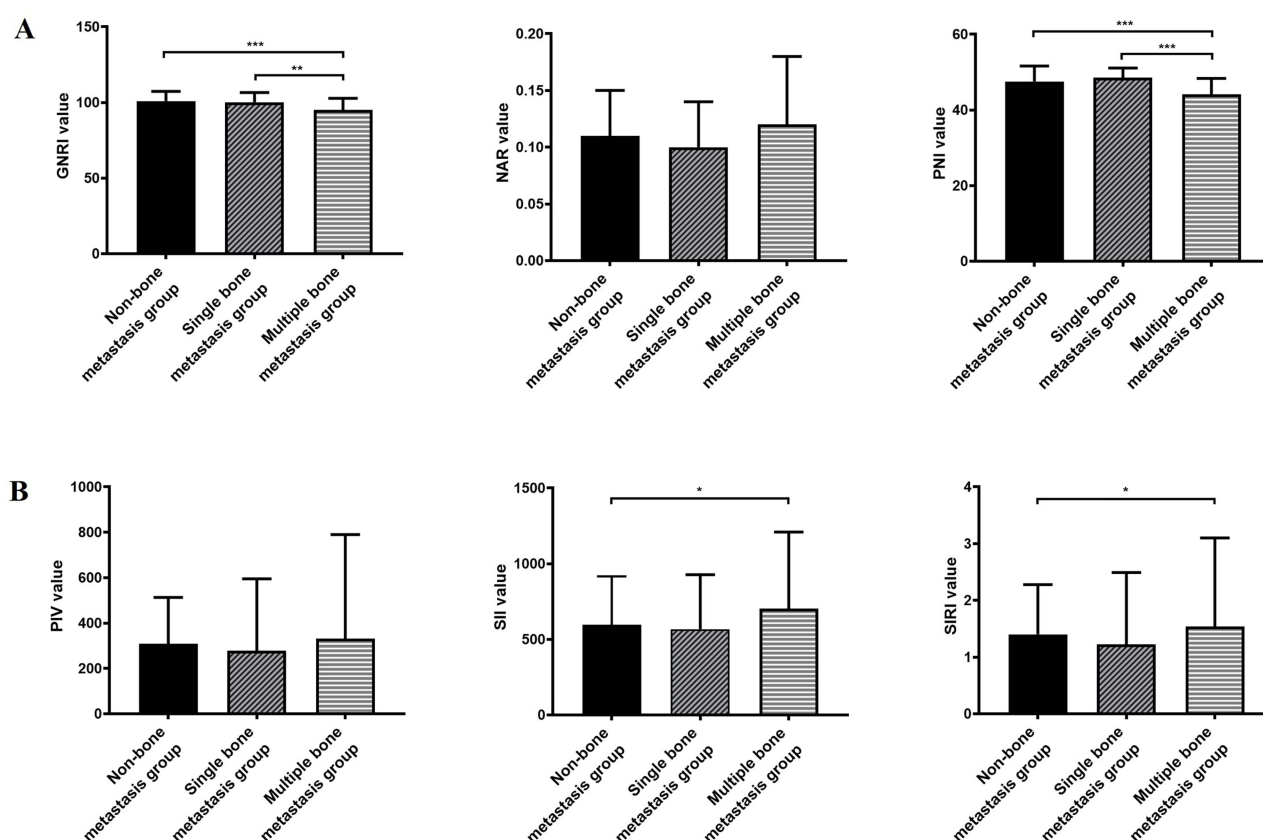

Figure 2 Comparison of nutritional status indices (GNRI, NAR, and PNI) (**A**) and comprehensive inflammatory indices (PIV, SII, and SIRI) (**B**) in prostate cancer patients with non-bone metastasis, single bone metastasis, and multiple bone metastasis.
Notes: *$P<0.05$; **$P<0.01$; ***$P<0.001$.
Abbreviations: GNRI, geriatric nutritional risk index; NAR, neutrophil to albumin ratio; PNI, prognostic nutritional index; PIV, pan-immune inflammation value; SII, systemic immune inflammation index; SIRI, system inflammation response index.
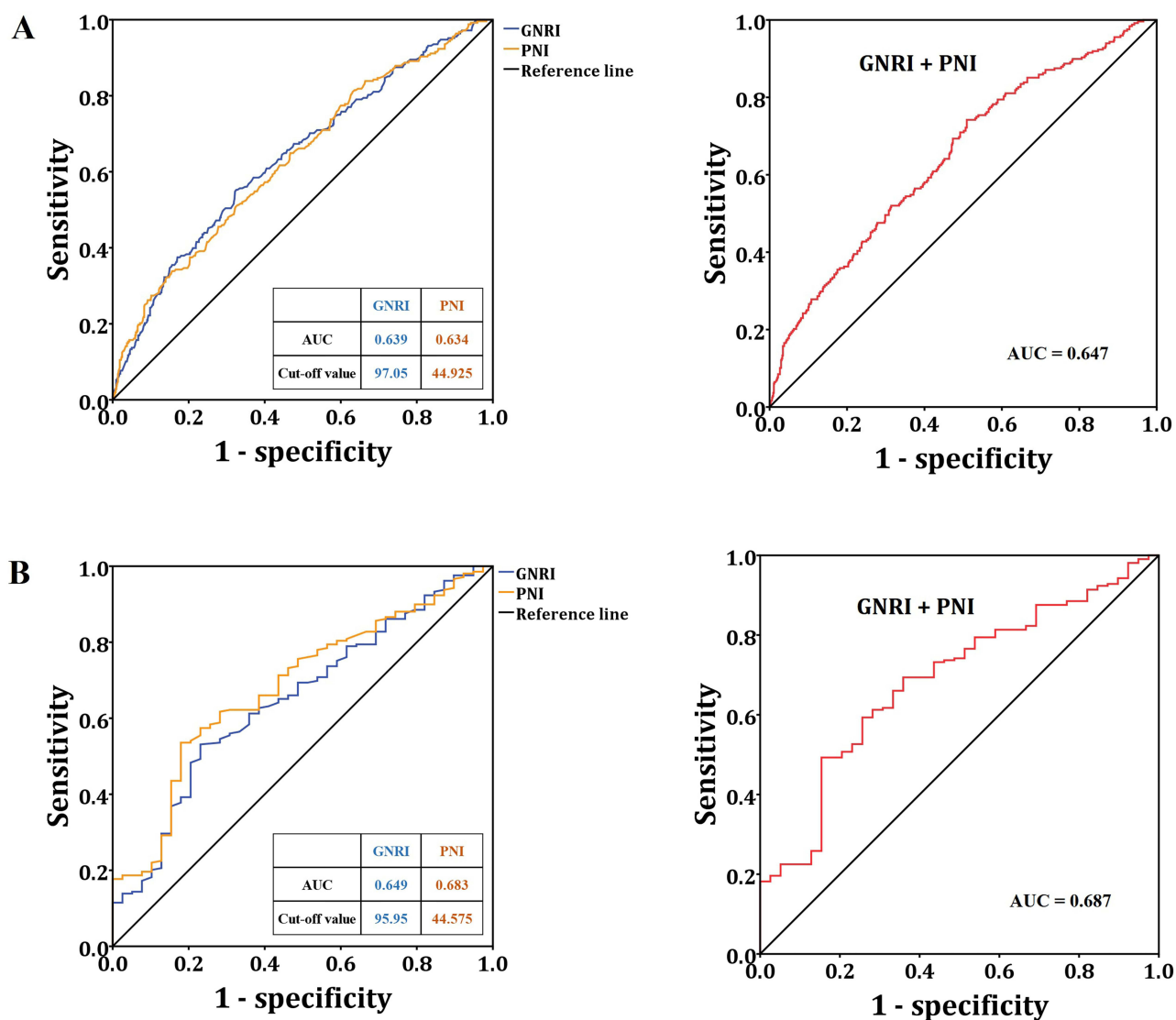
Figure 3 ROC analysis of GNRI and PNI used in the differential diagnosis of bone metastasis (**A**) and multiple bone metastasis (single bone metastasis as control) (**B**) in prostate cancer.
Abbreviations: GNRI, geriatric nutritional risk index; PNI, prognostic nutritional index; AUC, area under receiver operating characteristic curve.

Discussion

Inflammation and nutritional status related to malignant tumors have been one of the hot issues in recent years.[38] Tumor burden is not the only reason affecting the prognosis of tumor patients. Based on the differences in individual factors of patients with malignant tumors and the various biological characteristics of tumor cells themselves, there is still a large gap in the overall survival rate of patients at the same stage or using similar treatment programs.[39,40] Therefore, while continuing to focus on the characteristics of the tumor itself, constantly exploring the mechanism of tumor progression and updating treatment strategies,[41,42] more and more clinicians and researchers have paid attention to the study on the changes of TME[43] and the internal inflammation,[44] immunity, and nutritional status.[38] GNRI[45] and PNI[46] are new tumor prognostic indicators emerging in recent years.

Low GNRI was associated with poorer overall survival (OS)[47,48] and cancer-specific survival (CSS),[47,49] and disease-free survival (DFS)[48] in cancer patients. GNRI has been poorly studied in prostate cancer. Miao et al found that lower GNRI levels were associated with a higher risk of prostate cancer.[50] Shu et al revealed that GNRI was associated with postoperative complications of prostate cancer.[51] Some studies suggested that low GNRI was an independent risk of prostate cancer and

poorer OS[52–54] and PFS.[53] In this study, GNRI is considered to be a potential predictor of prostate cancer bone metastasis, and this study enriches the data on GNRI in prostate cancer metastasis.

PNI was a risk predictor of tumor metastasis of some cancers.[55–59] PNI was also associated with survival in patients with gastric cancer,[60,61] colorectal cancer,[62,63] cervical cancer,[64] NSCLC,[65] esophageal cancer,[25] pancreatic cancer,[59] and renal cell carcinoma.[66] Studies of PNI in prostate cancer are rarely reported. Some studies showed that PNI was a predictive marker of OS,[67–69] PFS,[67,69,70] and CSS[68,69] in prostate cancer patients. A lower PNI was a risk factor for a shorter recurrence time in prostate cancer patients after prostatectomy.[71] In this study, PNI may be a potential predictive indicator of prostate cancer bone metastasis.

Tumor metastasis depends on tumor angiogenesis and invasion of immune cells.[72] The site of tumor metastasis was rich in activated immune cells.[73] General speaking, the tumor microenvironment composed of the above cells is in a relatively stable state, and once the above homeostatic state is broken, tumor cell immune escape and cancer progression may occur. Tumor cells induce immune cells to promote the occurrence and development of bone metastasis, and immune cells may be potential therapeutic targets for bone metastasis.[74] Wang et al have established a prostate cancer bone metastasis prediction model based on multiple immune-inflammatory parameters.[75] However, in this study, PIV, SII, and SIRI were not effective in predicting the risk of bone metastasis of prostate cancer.

Immunoinflammatory response is involved in the development of tumor by changing the tumor microenvironment, affecting gene homeostasis, inducing tumor cell invasion and metastasis.[28,29] Lymphocytes and platelets are involved in tumor progression, while neutrophils can increase cancer cell invasion, proliferation, and metastasis, helping cancer cells evade immune surveillance.[76] Increased monocyte counts are associated with reduced overall survival from malignant tumors.[77,78] At present, the study of immunoinflammatory indices in prostate cancer mainly focuses on the relationship between these indices and prostate cancer risk and prognosis. A meta-analysis suggested that high SII may be associated with poorer OS and PFS.[79] Another meta-analysis showed that high SII was significantly associated with poorer OS; however, high SII level was not significantly associated with lymph node metastasis,[80] contrary to another study.[81] Some studies showed that high SII values were associated with an increased risk of prostate cancer.[82,83] The inflammatory response of prostate cancer is closely related to age, which may be associated with the common characteristics of cancer progression and aging, such as genomic instability, cellular senescence and chronic inflammation.[84] In addition, the interaction between aging and oxidative stress also plays an important role in the progression of tumors.[85] Furthermore, the results of this study show that the proportion of underweight (BMI<18.5) patients with bone metastasis than without. Generally speaking, overweight patients have higher levels of inflammation and may have a higher susceptibility to cancer. The opposite results obtained in this study may be related to the different sample sizes included and the differences among the populations.

The role of PIV, SII, and SIRI in prostate cancer metastasis has not been reported, while some studies have been reported in some other cancer types. High level of SII was associated with distant metastasis of colorectal cancer,[86] and renal cell carcinoma.[87] SII was associated with lymph node metastasis in patients with papillary thyroid cancer,[88,89] gastric cancer,[90–92] breast cancer,[93,94] and esophageal cancer.[95] However, there was no significant correlation between SII and lymph node metastasis of pancreatic cancer,[96] prostate cancer,[80] upper tract urothelial carcinoma.[97] This study found that PIV, SII, and SIRI had limited predictive efficacy in prostate cancer bone metastasis.

Among a panel of inflammation and nutritional markers, the GNRI and PNI performed best as a predictive factor of bone metastasis in patients with prostate cancer. However, this study still has the following limitations. First, as a retrospective study from a single medical institution, this research may have some methodological limitations, such as the problem of missing or incomplete patient information affecting the quality and completeness of the data, the inability to control the factors included in the analysis, which may affect the accuracy of the research results, and the restrictions on the selection of the included research subjects leading to the non-representativeness of the research subjects. Second, this study did not conduct stratified analysis of the correlation between the severity of bone metastasis, the number of metastasis and these indicators of prostate cancer. Third, the results of ROC curve analysis in this study showed that GNRI and PNI only had moderate predictive efficacy. The combination of GNRI and PNI with other indicators to comprehensively evaluate the risk of bone metastasis of prostate cancer may have better predictive efficacy. Finally, the molecular mechanism of these indicators in bone metastasis of prostate cancer patients was not thoroughly studied in this paper, and further research in animal experiments and clinical studies is needed.

Conclusions

In summary, prostate cancer is more common in older men, and about a quarter of patients have bone metastasis. Nutritional indicators (GNRI and PNI) based on albumin may have a good predictive effect on bone metastasis and multiple bone metastasis of prostate cancer. Of course, the true influence and role of GNRI and PNI in bone metastasis of prostate cancer require more research to reveal, especially the conclusions drawn from randomized controlled trials, systematic reviews, and meta-analyses. Furthermore, GNRI and PNI need to be combined with other indicators to enhance their clinical value.

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethics Approval and Consent to Participate

The study was approved by the Ethics Committee of Medicine, Meizhou People's Hospital. All participants signed informed consent in accordance with the Declaration of Helsinki.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors declare that they have no competing interests in this work.

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