Research paper

Risk factors for bone metastasis from renal cell cancer

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ARTICLE INFO

ABSTRACT

Objective: The prognosis for renal cell carcinoma (RCC) is related to a high rate of metastasis, including 30% of bone metastasis. In this study, we investigate the correlation between diverse clinical factors and bone metastases secondary from renal cell cancer (RCC), and to identify potential risk factors for bone metastasis in newly diagnosed patients and those who have already received treatment.

Methods: The clinical data of 372 patients with RCC were reviewed from January 2000 to August 2016. The correlations between age, gender, histopathologic types, alkaline phosphotase (ALP), CEA, AFP, CA-125, CA-153, CA-199, calcium, hemoglobin (HB) and bone metastases were analyzed. And the risk factors for bone metastases in RCC were identified by multivariate logistic regression analysis. The cutoff value, sensitivity and specificity of the independent correlation factors were calculated by receiver operating characteristic (ROC) curve.

Results: The bone is the second to the lung as a distant metastasis target site in patients with RCC. Thirty eight individuals were identified with bone metastases. Of these patients, significantly higher levels of ALP, calcium, HB were found than those without bone metastasis (P < 0.05, respectively). No significant differences were detected in CEA, AFP, CA-125, CA-153, CA-199, age, gender and histopathologic types between patients with and without bone metastases (P > 0.05, respectively). Multivariate logistic regression analysis indicated that ALP, calcium and HB were independent risk factors correlated with bone metastasis (P < 0.05, respectively). ROC curves demonstrated these factors had comparable accuracy at predicting bone metastasis (AUC were 0.749, 0.633 and 0.665, respectively). The cutoff values of ALP, calcium and HB were 105.5 U/L, 2.615 mmol/L and 111.5 g/L, respectively. The sensitivities of them were 57.9%, 36.8% and 71.1% for predicting bone metastasis, with specificities of 83.5%, 95.2% and 65.3%, respectively.

Conclusion: Based on our study, the concentrations of ALP, calcium and HB were potentially risk factors for bone metastasis in patients with RCC. For newly diagnosed patients, if the values of ALP > 105.5 U/L, calcium > 2.615 mmol/L and HB < 111.5 g/L were detected, intensive monitoring and bone scanning are warranted for them.

1. Introduction

Renal cell cancer (RCC) runs up to 3% of malignant tumors in human beings each year, and surgical resection of these tumors generally results in excellent long-term disease-free survival [1]. However, studies revealed that 20–50% of patients present with locally advanced and distant metastatic disease [2]. Moreover, patients with metastatic RCC (mRCC) of other organs represent an unfavorable subset of individuals. Especially the occurrence of the bone metastasis is widely accepted as a significant prognostic factor of life expectancy of patients [3].

Diagnosis of patients with bone metastasis currently primarily relies on plain X-ray, bone scanning, computed tomography (CT) and magnetic resonance imaging (MRI). The cost of these tests is expensive and early bone metastatic lesions may not be easily detected by imaging studies [4,5]. Given that, the early discovery of the occurrence of bone metastases will significantly influences the choice of RCC treatment. Identifying readily available and valuable risk factor is a meaningful clinical benefit for timely intervention to prevent and delay bone metastasis. Furthermore, these risk factors could help to avoid bone scanning and intensive monitoring for patients at a low risk of bone metastasis [5].

Many studies have attempted to identify risk factors of progression, prognosis and reaction to therapy in the patients with bone metastasis.

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Recently, several serum tumor markers, including alkaline phosphate (ALP) [6], calcium [7] and hemoglobin (HB) [8] have been extensively investigated and considered to be potentially predictive or prognostic factors for patients with bone metastases from cancer. However, risk factors for bone metastasis from RCC had been examined in a few studies and some results remained controversial. There are still no standard definition of risk factors and cut-off levels specifically [9]. The purpose of the current study was to investigate the correlation between clinical–pathological parameters, biomarkers, and bone metastases in RCC at the time of diagnosis, and to identified some independent risk factors for definition of patients with RCC at 'high risk' of bone metastases.

2. Materials and methods

2.1. Patient selection

This study was approved by the medical research ethics committee of the First Affiliated Hospital of Nanchang University.

A retrospective study was carried out and a series of consecutive patients with RCC between January 2000 and August 2016 were included in this study. All the patients were confirmed with primary RCC based on the histopathologic analysis of specimens obtained by needle biopsy or radical nephrectomy. And bone metastases were diagnosed by bone scanning and other organs metastases was diagnosed by plain X-ray, CT or MRI. Patients presenting with concomitant pathologies that could potentially affect the evaluation of the risk factors were excluded from this study, such as bone metabolic disorders, hyperparathyroidism, hepatic dysfunction and other malignant tumors.

2.2. Data collection

Demographics and clinical characteristics of patients in this study included: patients' age at diagnosis of the primary tumor, gender, treatment for RCC, histopathologic types, metastases sites, laboratory findings at diagnosis of the primary tumor, such as ALP (140 U/L was considered to be the upper normal limit), calcium (2.6 mmol/L was considered to be the upper normal limit) and HB, common tumor markers (serum CEA, AFP, CA125, CA153 and CA199 values were determined in the same laboratory, the normal range was 0–6.5 ng/ml, 0–7 ng/ml, 0–35 U/ml, 0–25 U/ml, 0–27 U/ml, respectively). All the above factors were retrospectively collected and reviewed. The correlation between clinical parameters and bone metastases was analyzed, and the risk factors for bone metastases in RCC were identified.

2.3. Statistical analysis

Quantitative variables were reported as means ± standard deviation and compared with Independent sample t-test or Univariate analysis. Qualitative variables were expressed as numbers and percentages, and were assessed by the Chi-square test. The independent risk factors related to bone metastases were analyzed by Multivariate logistic regression analysis model. The sensitivity and specificity were calculated based upon optimal cut off scores. Accuracy was determined by the area under the curve (AUC), calculated from receiver operating characteristic (ROC) curves. Statistical significance was set as P value less than 0.05. All analysis was performed by IBM SPSS Version 22 (SPSS Inc. Chicago IL).

3. Results

3.1. Patient demographics

A total of 372 patients with RCC were included in this study. The patients' demographics were demonstrated in Table 1. The majority of the patients were man (233 cases, 62.6%) and most of the

Table 1
Baseline characteristics of patients with RCC.

Patient characteristics	n (%)
Primary site	
Right	183(49.2)
Left	188(50.5)
Bilateral	1(0.3)
Age at diagnosis(years)	
Median	56
Range	3–86
Gender	
Man	233 (62.6)
Female	139 (37.4)
Histopathological type, n (%)	
Clear cell	280 (75.3)
Chromophobe	24 (6.4)
Papillary	24 (6.4)
Multilocular cystic	10 (2.7)
Other	11 (3)
Sarcomatoid	7 (1.9)
Undifferentiated	8 (2.2)
Granular cell	6 (1.6)
Radiological diagnosis	2 (0.5)
No. of patients with mRCC	111
Gender	
Man	76 (68.5)
Female	35 (31.5)
Site of metastases	
Lung	41 (36.9)
Bone	38 (34.2)
Lymph node	37 (33.3)
Liver	12 (10.8)
Brain	5 (4.5)
Adrenal	4 (3.6)
Other	26 (23.4)

Note: RCC, renal cell carcinoma; mRCC, metastases RCC.

histopathologic types of them were clear cell carcinoma (280 cases, 75.3%). Of these patients, 111 patients with mRCC were identified. The distribution of metastatic organs was demonstrated in Table 1.

3.2. The metastatic organs and sites of RCC in patients with different ages

The rate of old patients with mRCC was higher than that of young patients (58.6% vs 41.4%, young patients defined as individuals aged < 55 years [10]). For the metastatic organs second from RCC, young patients were easy to get bone and lymph node metastases. However, lung metastases were more common in old patients. The number of patients with single site metastases was larger than those patients with two or more metastatic sites (67 cases vs 44 cases). And the rate of patients with concomitant metastases decreased as age increasing (Table 2).

3.3. Distribution of bone metastases from RCC

The bone was second to the lung as a distant metastasis target site in patients with RCC. We detected 38 patients with bone metastases in this

Table 2
The metastatic organs and sites of RCC in patients with different ages.

	Overall	< 55 years	≥55 years	$\chi2$	P-value
No. of mRCC patients	111	46(41.4)	65(58.6)	–	–
Lung	41(36.9)	15(32.6)	26(40)	0.632	0.427
Bone	38(34.2)	19(41.3)	19(29.23)	1.744	0.187
Lymph node	37(33.3)	21(45.7)	16(24.6)	5.364	0.021
No. of metastatic sites					
1	67(60.4)	17(36.9)	38(58.5)	3.936	0.047
≥2	44(39.6)	29(63.1)	27(41.5)		

Note: Patients, n (%) (N = 111).

Table 3
The distribution of bone metastases in patients with RCC.

Patient characteristics	Patients, n(%)(N = 38)
Site of bone metastases	
Spine	
Cervical	3 (7.9)
Thoracic	15 (39.5)
Lumbar	14 (36.8)
Ribs	9 (23.7)
Pelvis	10 (26.3)
Femur	6 (15.8)
Humerus	4 (10.5)
Skull	2 (5.2)
Sternum	2 (5.2)
Clavicle	1 (2.6)
Histopathological type, n (%)	
Clear cell	32 (84.3)
Undifferentiated	3(7.9)
Chromophobe	1(2.6)
Papillary	1(2.6)
Other	1(2.6)
Gender	
Man	29(76.3)
Female	9(23.7)

study, most of them were man 29(76.3%) and 84.3% of the histo-pathologic type was clear cell carcinoma. The most common affected sites were the spine, including cervical 3 cases (7.9%), thoracic 15 cases (39.5%) and lumbar 14 cases (36.8%), followed by ribs 9 (23.7%) and pelvis 10 (26.3%) (Table 3).

3.4. The concentrations of biomarkers and clinical–pathological parameters in patients with and without bone metastases

The differences between patients with and without bone metastases on biomarkers and clinical-pathological parameters were analyzed. The results revealed that patients with bone metastases from RCC were associated with the concentrations of ALP, calcium and HB, because significant differences were found for these factors between patients with and without bone metastases ($P < 0.05$, respectively) (Table 4), These results indicated that the serum concentration of ALP, calcium and HB was potentially related to the bone metastases in patients with

Table 4
The correlation between diverse clinical factors and bone metastases.

Factors	BM	NBM	t/$\chi 2$ value	P value
Age	55.61 ± 13.48	56.11 ± 14.40	0.204	0.839
CEA	34.18 ± 113.59	3.00 ± 3.54	0.990	0.342
AFP	2.68 ± 1.17	3.47 ± 6.07	0.225	0.823
CA-125	31.09 ± 25.40	62.10 ± 236.65	0.451	0.653
CA-153	15.00 ± 7.97	16.50 ± 18.24	0.251	0.803
CA-199	69.69 ± 206.55	19.73 ± 24.60	0.837	0.420
ALP	236.68 ± 464.14	81.48 ± 60.36	2.059	0.047
HB	103.24 ± 24.27	117.39 ± 25.17	3.295	0.001
Calcium	2.48 ± 0.48	2.28 ± 0.25	2.474	0.018
Gender	38	334	3.385	0.066
Man	29	204		
Female	9	130		
HT	38	334	12.429	0.133
Clear cell	32	248		
Chromophobe	1	23		
Papillary	1	23		
Multilocular cystic	0	10		
Other	1	10		
Sarcomatoid	0	7		
Undifferentiated	3	5		
Granular cell	0	6		
Radiological	0	2		

BM: Bone metastasis; NBM: No bone metastasis; ALP: alkaline phosphotase; HB: hemoglobin; HT: histopathological types.

Table 5
Multivariate logistic regression models analysis the risk factors of bone metastasis from RCC.

Factors	β	OR	OR(95% CI)	$\chi 2$	P
ALP	0.895	2.488	1.491–4.02	12.52	< 0.001
Calcium	0.828	2.289	1.088–4.817	4.758	0.029
HB	−1.196	0.302	0.125–0.729	7.1	0.008

CI: confidence interval; OR: odds ratio; β: coefficient of regression; RCC: renal cell carcinoma.

RCC. No significant difference was found on other factors between patients in the two groups ($p > 0.05$).

3.5. The risk factors of bone metastases in RCC

Additionally, multivariate logistic regression models analysis was carried out to identify the potential risk factors for bone metastases in RCC. The results showed that the concentrations of ALP (OR 2.488, 95% CI: 1.491–4.02, P < 0.001), calcium (OR 2.289, 95% CI: 1.088–4.817, P = 0.029) and HB (OR 0.302, 95% CI: 0.125–0.729, P = 0.008 were the independent risk factors correlated with bone metastases in patients with RCC (Table 5).

3.6. Values of risk factors for predicting bone metastases

Figs. 1–3 shows the ROC curves of ALP, calcium and HB for predicting the risk of bone metastasis. These factors had comparable accuracy on predicting bone metastasis from RCC (the AUC of those factors were 0.749, 0.633 and 0.665, respectively). The cutoff values of those factors were 105.5 U/L, 2.615 mmol/L and 111.5 g/L, respectively. The calcium had a higher specificity (95.8%) among these three factors, and the HB had a higher sensitivity (71.1%) among these three factors. Additionally, combined ALP, HB with calcium had higher specificities (HB + ALP: 91.0%; HB + calcium: 97.6%; ALP + calcium: 97.9%; HB + calcium + ALP: 98.2%) compared to one single factor (Table 6).

4. Discussion

Renal cell carcinoma (RCC) is a kind of malignancy arising from the
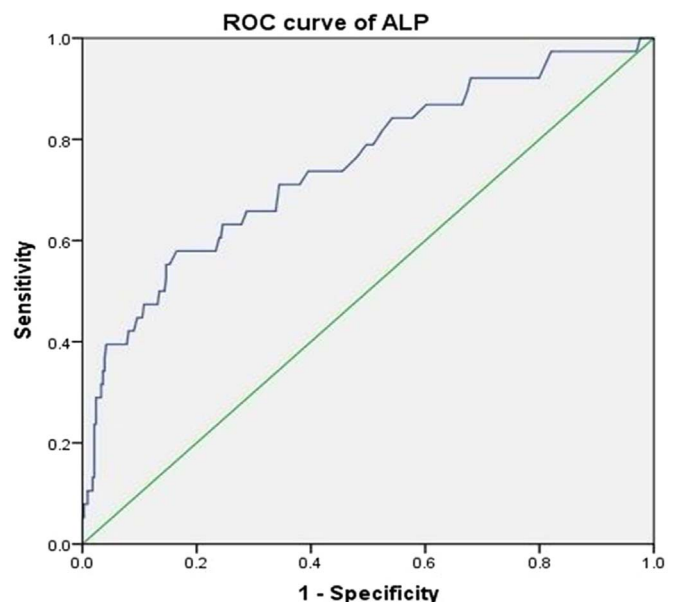

Fig. 1. Receiver operating characteristic (ROC) curve demonstrated sensitivies and specificities of the concentrations of ALP for predicting the risk of bone metastasis.
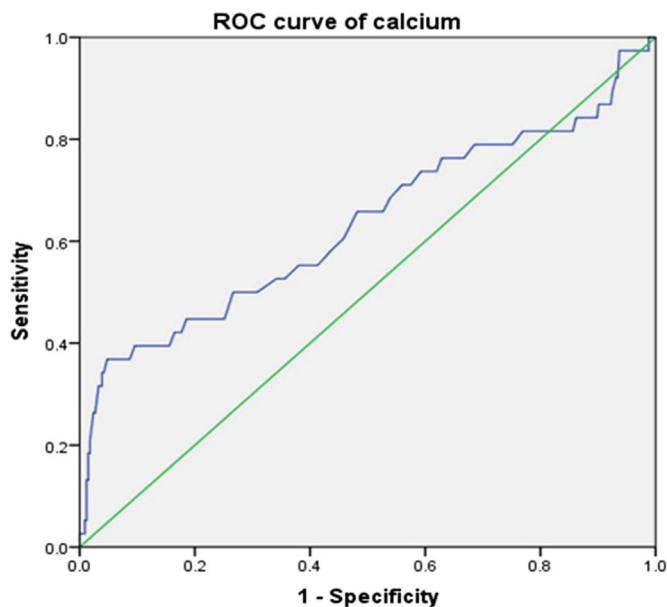
Fig. 2. Receiver operating characteristic (ROC) curve demonstrated sensitivities and specificities of the concentrations of calcium for predicting the risk of bone metastasis.
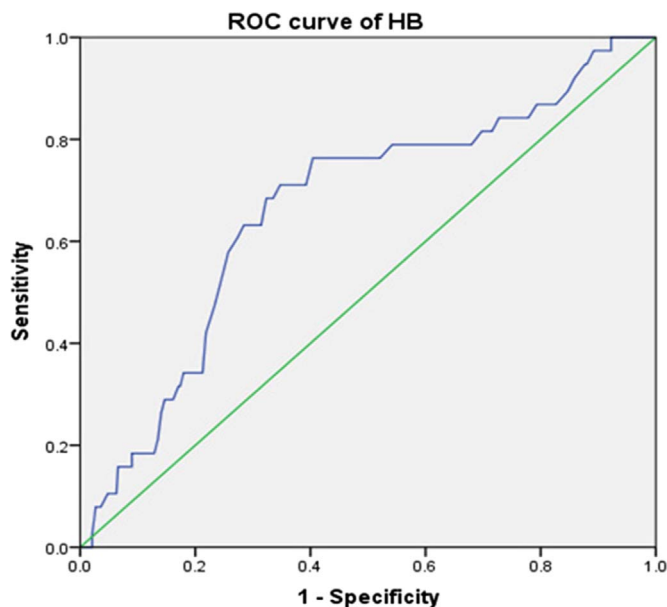

Fig. 3. Receiver operating characteristic (ROC) curve demonstrated sensitivities and specificities of the concentrations of HB for predicting the risk of bone metastasis.

epithelium of renal tubules. About one-third of patients with advanced RCC have bone metastasis that are often osteolytic and cause substantial morbidities, such as pain, pathologic fracture, spinal cord

compression and hypercalcemia. And the presence of bone metastasis in RCC is usually associated with poor prognosis [9]. Bone-targeted treatment using bisphosphonate and denosumab can reduce bone complications in RCC, but does not cure the disease or improve survival rate [11]. Therefore, identifying readily available and valuable predictive factors is a meaningful benefit for timely intervention to prevent and delay bone metastasis. For the incidence of bone metastases from RCC, previous studies have established that around one third of patients developed bone involvement [9]. In the present study, we identified 111 individuals with mRCC, and the most common sites of metastases were lung (36.9%), followed by bone (34.2%). The frequency of metastasis sites in our study was consistent with previous studies [9,10].

Due to the lack of consensus about the effect of age on bone metastases from RCC [10,12], we analyzed the correlation between age at diagnosis and the distribution of metastatic organs. Similar to previous studies, the number of single site metastases was greater than those of two or more sites [8]. And younger patients were more likely to have high incidences of bone and lymph node metastases. However, there was no statistically significant correlation between age and bone metastases in these patients, which implies that age is not a high risk of bone metastases in RCC.

For bone metastases sites, the most common one was the spine in our study: including cervical (7.9%), thoracic (39.5%) and lumbar spine (36.8%), followed by pelvis (26.3%) and ribs (23.7%). The distribution of bone metastases was mainly in the axial skeleton, which was in line with previous studies [10]. Previous studies have shown patients with the metastatic site in axial skeleton had a relative lower survival rate than those with appendicular skeleton metastases [13]. Therefore, making clear of the distribution of bone metastases sites is helpful to know the prognosis of patients with RCC.

Total serum alkaline phosphatase (ALP) presents in many human tissues and partly reflects osteoblastic activity, which is more pronounced in patients with larger volume and aggressive skeleton metastatic disease [14]. Significant differences were found for both total ALP and bone-special ALP levels between patients with and without bone metastases. And it could help to avoid PET-CT/bone scanning and intensive monitoring for patients at a low risk of bone metastasis [15]. Sun et al. revealed bone ALP as a surrogate marker of bone metastasis in gastric cancer patients [6]. Rao et al. demonstrated tumor-derived ALP regulates tumor growth, epithelial plasticity and disease-free survival in metastatic prostate cancer [16]. Chen et al. indicated the serum concentrations of ALP > 100.5 u/l was identified to be the risk factors for bone metastases in patients with breast cancer [14]. In consistence with previous studies, our study indicated that serum ALP was an independent risk factor for bone metastasis in patients with RCC. The cutoff value of it was 105.5 U/L, and the sensitivity and specificity were 57.9% and 83.5%.

For human body, the majority of calcium is stored in bone, and the concentration of it is under strictly hormonal regulation at the levels of resorption in the kidneys, mobilization from the skeleton and intestinal absorption. Joeckel et al. revealed that high calcium concentration promoted migration and proliferation of bone metastasis in RCC via enhanced expression of calcium-sensing receptor [7]. Boudot et al.

Table 6
The cutoff value, sensitivity and specificity of ALP, HB and calcium for predicting bone metastasis.

Factors	Cutoff value	Sensitivity (%)	Specificity (%)	AUC	95% CI
ALP	105.5 U/L	57.9	83.5	0.749	0.659–0.839
Calcium	2.615 mmol/L	36.8	95.2	0.633	0.522–0.745
HB	111.5 g/L	71.1	65.3	0.665	0.573–0.758
HB + ALP		47.4	91.0		
HB + CA		34.2	97.6		
ALP + CA		28.9	97.9		
HB + CA + ALP		28.9	98.2		

CA: Calcium.

indicated that high expression of calcium and calcium-sensing receptor concentration was found to be correlated with the formation of bone metastases in breast cancer [17]. Also, Breuksch et al. showed that calcium played a significance role in the formation of bone metastasis and should be taken into consideration when planning therapeutic strategies for preventing bone metastasis [18]. In line with previous studies, the results of our study showed significant difference in the serum concentrations of calcium between patients with and without bone lesions, and we identified the serum levels of calcium was an independent risk factor correlated with bone metastasis. The cut off value of it was 2.615 mmol/L. These findings indicated that extracellular calcium concentration > 2.615 mmol/L was a risk factor for bone metastasis in patients with RCC.

Previous studies suggested that HB was not only a useful marker for tumor aggressiveness, but also a prognostic factor for distant metastasis [19]. Furthermore, Kawai et al. revealed that HB was a factor of specifically promoting bone metastasis from prostate cancer [20]. Huang et al. showed that the serum concentration of HB was independent risk factors for bone metastases in patients with bladder cancer [8]. In the current study, we identified the concentrations of HB as an independent risk factor correlated with bone metastasis. The cutoff value of it was 111.5 g/L. It suggested that the serum hemoglobin levels < 111.5 g/L could help to distinguish populations at a higher risk of bone metastases from RCC.

Compared to the single factor of ALP, calcium and HB, we found that combined ALP, HB with calcium had higher specificities for predicting bone metastases in RCC. It suggested that combination of risk factors appeared to be more useful for predicting bone metastasis and may provide important information for patients with RCC.

To our knowledge, we are successful at identifying the concentrations of ALP, calcium and HB as independent bone metastasis-associated risk factors in RCC cases. Although the results were interesting, the limitations of this study still needed to be discussed. First, it was a retrospective study with insufficient data, which made some patients to be excluded from this study and may affect the analysis results of the study. Second, we just collected the data of patient with RCC at the time of diagnosis, and some data such as patients' survival rate and follow up were not included in it. Third, the sample size in this study was relative small and just came from a single institution, which may affect the results. Thus, a prospective, multi-center study is needed to verify the results of our study.

5. Conclusions

Based on the present study, we have established that around one third of patients with metastases RCC developed bone involvement, and the most frequent sites of bone metastases were spine. Additionally, the concentrations of calcium, ALP, and HB were potentially risk factors for bone metastasis in patients with RCC. For newly diagnosed patients, if the values of ALP > 105.5 U/L, calcium > 2.615 mmol/L and HB < 111.5 g/L were detected, intensive monitoring and bone scanning are warranted for them. However, due to the small sample size and just a retrospective analysis of this study, future study with a prospective, a large sample size and multiple centers analysis is needed to verify the results of this study.

Acknowledgements

Disclosure

None of the authors have received payment or services from a third party (government, commercial, private foundation, etc) for any aspect of the submitted work at any time. The authors report no conflicts of interest in this work.

Authors' contribution

The first and second author (Xuan-Yin Chen and Min Lan) contributed equally to this study and share the first authorship.

Conflicts of interest

No benefits in any form have been or will be received from any commercial party related directly and indirectly to the subject of this manuscript.

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