Intensive Care Research (2023) 3:95–102
https://doi.org/10.1007/s44231-022-00025-0

RESEARCH ARTICLE

Clinical Features and Prognosis of Severe Secondary Hyperparathyroidism: A Retrospective Study from a Single Center

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Received: 25 April 2022 / Accepted: 23 November 2022 / Published online: 30 November 2022

Abstract

Purpose Secondary hyperparathyroidism (SHPT) is one of the most common complications of chronic kidney disease and has a high rate of morbidity and mortality. Current studies on prognostic factors in SHPT are inadequate. We aimed to identify a single-center cohort of severe SHPT to elucidate relevant clinical and laboratory features and explore laboratory indicators that related to its prognosis.

Methods The clinical data of 46 patients with SHPT, admitted to the intensive care unit (ICU) of the First Affiliated Hospital of Zhengzhou University in the time period ranging from January 2019 to March 2022 were analyzed retrospectively. Clinical data collected were screened univariately for influences that were associated with poor prognosis. A binary logistic regression model was constructed to analyze the independent risk factors for poor clinical prognosis, using correlated influences. The value of each indicator in predicting patient prognosis was analyzed using receiver operating characteristic curves (ROC) curves.

Results The causes of death among the 46 patients with severe SHPT were cardiogenic death (malignant arrhythmia, cardiac arrest) in 11 cases (47.8%), sepsis in 9 cases (39.2%), and neurogenic death (intracranial hemorrhage) in 3 cases (13.0%). Patients were divided into a good prognosis group and a poor prognosis group according to their status at the time of leaving the ICU. There was no statistically significant difference in sex, BUN, NT-pro BNP, ALP, Scr, Mg, Ca, Pi, K, CRP, Hb, and PLT between the poor prognosis group and the good prognosis groups. The age, PTH, PCT, WBC, APACHE II, and neutrophil ratio of the poor prognosis group were higher than those of the good prognosis group, and the ALB level was lower than that of the good prognosis group, with a statistically significant difference of $P < 0.05$. The 19 clinical indicators mentioned above were screened univariately. Among them, age, PTH, WBC, ALB, APACHE II and neutrophil ratio were significantly associated with prognosis, $P < 0.05$. Binary logistic regression analysis showed that age (OR = 1.076, 95% CI (1.011, 1.145)), PTH (OR = 1.004, 95% CI (1.000, 1.007)), WBC (OR = 1.295, 95% CI (1.026, 1.634)) were indicators for poor prognosis in patients with severe SHPT, and ALB (OR = 0.803, 95% CI (0.645, 0.998)) was a protective factor for poor prognosis. The ROC curve showed that the optimal cut-off point for patient age was 51 years, with a sensitivity of 86.9% and specificity of 52.2%; the optimal cut-off point for PTH was 346 pg/ml, with a sensitivity of 59.1% and specificity of 82.6%; the optimal cut-off point for WBC was 11.95 × 10^9/L, with a sensitivity of 56.52% and specificity of 91.3%; the optimal cut-off point for neutrophil ratio was 82.4%, sensitivity 82.6%, specificity 73.9%.

Conclusion Age, PTH, and WBC are independent risk factors for poor prognosis of severe SHPT, and ALB is an independent protective factor for poor prognosis. Patients with severe SHPT should be assessed for risk of the poor prognosis based on age, admission PTH, WBC, ALB, and neutrophil ratio as early as possible to adjust the treatment strategy.

Keywords Critical illness · Secondary hyperparathyroidism · Sepsis · Cardiac death · Prognosis

1 Introduction

Secondary hyperparathyroidism (SHPT) is one of the most common complications of chronic kidney disease (CKD). According to epidemiological survey statistics, the prevalence of chronic kidney disease in China is 10.8%, and the

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trend is increasing [1]. It is estimated that there are about 119.5 million patients with chronic kidney disease in China [2]. About 32% of patients with chronic kidney disease eventually progress to refractory or severe SHPT [3]. Elevated PTH involves various systems throughout the body, causing multisystem complications [4], resulting in adverse clinical events such as malnutrition, anemia, vascular and cardiac valve calcification, renal-type bone disease, restless leg syndrome, pruritus and ectopic calcification [5]. Increased mortality from cardiovascular events and all-cause mortality has been reported in patients with chronic kidney disease [6–9]. Patients with SHPT have more comorbidities and poorer nutritional status, and their prognosis is extremely poor in case of adverse events such as cardiovascular and cerebrovascular accidents and sepsis. However, most of the current studies on SHPT have focused on the effects of various treatment modalities when the disease is stable [10–12]. There is a lack of studies on severe SHPT and a lack of reports on prognostic-related predictors of severe SHPT. An accurate assessment of the prognosis of SHPT patients at the time of admission would be extremely important for the treatment plan after admission. This study analyzed the data of 46 SHPT patients admitted to the First Affiliated Hospital of Zhengzhou University ICU from January 2019 to March 2022 to investigate the clinical characteristics, laboratory indices and factors influencing the prognosis of critically ill patients SHPT. The aim was to improve the understanding of critical SHPT and provide evidence for early intervention.

2 Materials and Methods

2.1 Study Patients

The case of 46 patients admitted to ICU of the First Affiliated Hospital of Zhengzhou University with secondary hyperparathyroidism between January 2019 and March 2022 were collected. This study was approved by the Ethics Committee of the First Affiliated Hospital of Zhengzhou University. The ethics number is: 2022-KY-1303–004.

2.2 Inclusion and Exclusion Criteria

The inclusion criteria in this study were as follows: (1) ICU treatment for ≥ 1d; (2) The primary diagnosis includes both chronic kidney disease (Glomerular filtration rate < 60 ml/min·1.73m^2 for > 3 months) and secondary hyperparathyroidism (①. Combination of primary diseases causing hypocalcemia or hyperphosphatemia, such as chronic renal failure, renal osteodystrophy.; ②. PTH > 65 pg/ml); (iii) Meet at least one of the following three (① PTH > 800 pg/ml;② Presence of significant bone changes such as, Sagliker syndrome or regression man syndrome;③ Development of other life-threatening complications due to SHPT).

Exclusion criteria: (1) primary hyperparathyroidism; (2) acute renal failure; (3) hospitalization records resulting from fatal events such as car accidents and trauma; (4) primary cardiovascular and cerebrovascular diseases. (5) Patients who have already undergone parathyroidectomy.

2.3 Data Collection

Basic patient information and diagnoses were collected at the time of admission. First biochemical examination and results of electrolyte indicators after admission were collected: procalcitonin (PCT), C reactive protein (CRP), white blood cell (WBC), parathyroid hormone (PTH), N-terminal pro-B type natriuretic peptide (NT-pro BNP), alkaline phosphatase (ALP), blood creatinine (Scr), blood urea nitrogen (BUN), Serum albumin(ALB), Hemoglobin(Hb), platelet(PLT), serum ferritin(SF),Serum calcium(Ca),Serum phosphorus(Pi),Serum potassium(K),Serum magnesium(Mg). The patient's ICU stay, discharge diagnosis and prognosis at the time of ICU discharge were recorded. Patients were divided into a good prognosis group and a poor prognosis group (including those who were critically ill and whose families requested discharge) according to their status at the time of leaving the intensive care unit. There were 23 cases in the good prognosis group, 16 males and 7 females; 23 cases in the poor prognosis group, 13 males and 10 females. Primary diagnosis in the poor prognosis group: 11 cases (47.8%) of cardiogenic death (malignant arrhythmia, cardiac arrest, etc.), 9 cases (39.2%) of sepsis, and 3 cases (13.0%) of neurogenic death (intracranial hemorrhage).

2.4 Statistical Analysis

SPSS 28.0 statistical software was used for data processing. One-sample K-S test (two-sided test) was used to determine whether the measurement data conformed to a normal distribution, and those conforming to a normal distribution were expressed as $\bar{x} \pm s$. Independent samples t-test was used for comparison between two groups. Non-normally distributed measures were expressed using M (P25, P75), and the Mann–Whitney U test was used for comparison between the two groups. Count data were analyzed using a four-cell table or row × list $\chi 2$ tests. Independent risk factors and protective factors for prognosis were screened for the presence of poor prognosis (death or automatic discharge) as the outcome variable, the independent variables of laboratory indicators were collected as described above, and a logistic regression model was established with the Backward-LR method of indicator entry, with the exclusion criterion set at 0.1 and

the inclusion criterion set at 0.05. Independent risk factors for poor prognosis were screened out. The sensitivity, specificity and maximum Youden index boundaries of each entry index were analyzed using receiver operating characteristic curves (ROC). A test level of $p < 0.05$ was used to indicate a statistically significant difference.

3 Results

3.1 Clinical Features

Table 1 summarizes the clinical characteristics of the two groups of SHPT patients. Among them, there was no statistically significant difference in sex, BUN, NT-pro BNP, ALP, Scr, Mg, Ca, Pi, K, CRP, Hb, and PLT between the poor prognosis group and the good prognosis group. The mean age increased by 10.217 years in the poor prognosis group compared to the good prognosis group. Simultaneously the PTH (485 > 184), PCT (1.98 > 0.80), WBC (12.7 > 7.0), APACHE II score (21 > 13) and neutrophil ratio (88.9% > 77.4%) were higher in the poor prognosis group than in the good prognosis group. In contrast, the mean ALB level in the poor prognosis group decreased by 4.345 g/L compared to the good prognosis group, and the differences were all statistically significant, $P < 0.05$ (Fig. 1).

3.2 Binary logistic regression analysis affecting prognosis Predictive Value

The prognostic status at discharge was used as the dependent variable, and values were assigned: good prognosis = 0, poor prognosis = 1. The 19 clinical indicators mentioned above (sex, age, PTH, BUN, NT-pro BNP, ALP, Scr, Mg, Ca, Pi, K, PCT, CRP, WBC, ALB, Hb, PLT, neutrophil ratio, APACHE II) were screened univariately. Among them, age, PTH, WBC, ALB, APACHE II and neutrophil ratio were significantly associated with prognosis, $P < 0.05$. Five variables significantly associated with prognosis (age, PTH, WBC, ALB, and neutrophil ratio) were used as independent variables, and prognostic status at discharge was used as the dependent variable. Binary logistic regression analysis was performed using the Backward-LR method. The results showed that age, PTH and WBC were independent risk factors for poor prognosis and ALB was an independent protective factor for poor prognosis (Table 2). The values of Cox & Snell R-square and Nagelkerke R-square at model pooling were 0.509 and 0.679, respectively, the overall validation rate of the model was 77.8% correct.

3.3 The Value of Observational Indicators at Admission to Predict Prognosis

The ROC was used to evaluate the predictive value of related indicators in ICU poor prognosis, and the area under curve (AUC), sensitivity, specificity and Youden

Table 1 Clinical characteristics of patients with severe SHPT in the ICU in the good prognosis group compared with the poor prognosis group

Clinical Features	Poor prognosis group (23 cases)	Good prognosis group (23 cases)	Statistical values	Sig
Gender				
Male	13	16	$X^2 = 0.840$	0.359
Female	10	7		
Age	60.43 ± 18.80	50.22 ± 13.85	t = -2.098	0.042
PTH	485.00 (128.50,1197.50)	194.00 (116.00,289.00)	Z = −2.089	0.037
BUN	22.65 (19.08,26.80)	21.90 (18.80,34.90)	Z = −0.099	0.921
NT-pro BNP	19,281.00 (12,187.00,35,000)	27,309.60 (6855.00,45,997.00)	Z = −0.594	0.552
ALP	111.00 (75.00,250.00)	113.00 (77.00,164.00)	Z = −0.110	0.913
Scr	696.00 (474.00,820.00)	612.20 (490.00,901.90)	Z = −0.330	0.742
Mg	1.02 ± 0.16	0.93 ± 0.17	t = −1.703	0.096
Ca	2.01 (1.89,2.15)	2.04 (1.97,2.21)	Z = −0.560	0.575
Pi	1.90 (1.33,2.70)	1.80 (1.60,1.98)	Z = −0.978	0.328
K	4.57 ± 0.78	4.45 ± 1.01	t = −0.437	0.664
PCT	1.98 (0.81,13.28)	0.80 (0.30,1.29)	Z = −2.56	0.01
CRP	44.40 (17.30,135.49)	12.56 (6.82,100.08)	Z = −1.336	0.181
WBC	12.71 (7.20,14.86)	7.00 (4.87,10.87)	Z = −2.955	0.003
ALB	28.15 ± 6.97	32.50 ± 6.15	t = 2.240	0.03
Hb	89.88 ± 22.03	87.14 ± 24.27	t = −0.402	0.69
APACHE II	21 (15,25)	13 (10,16)	Z = −2.826	0.005

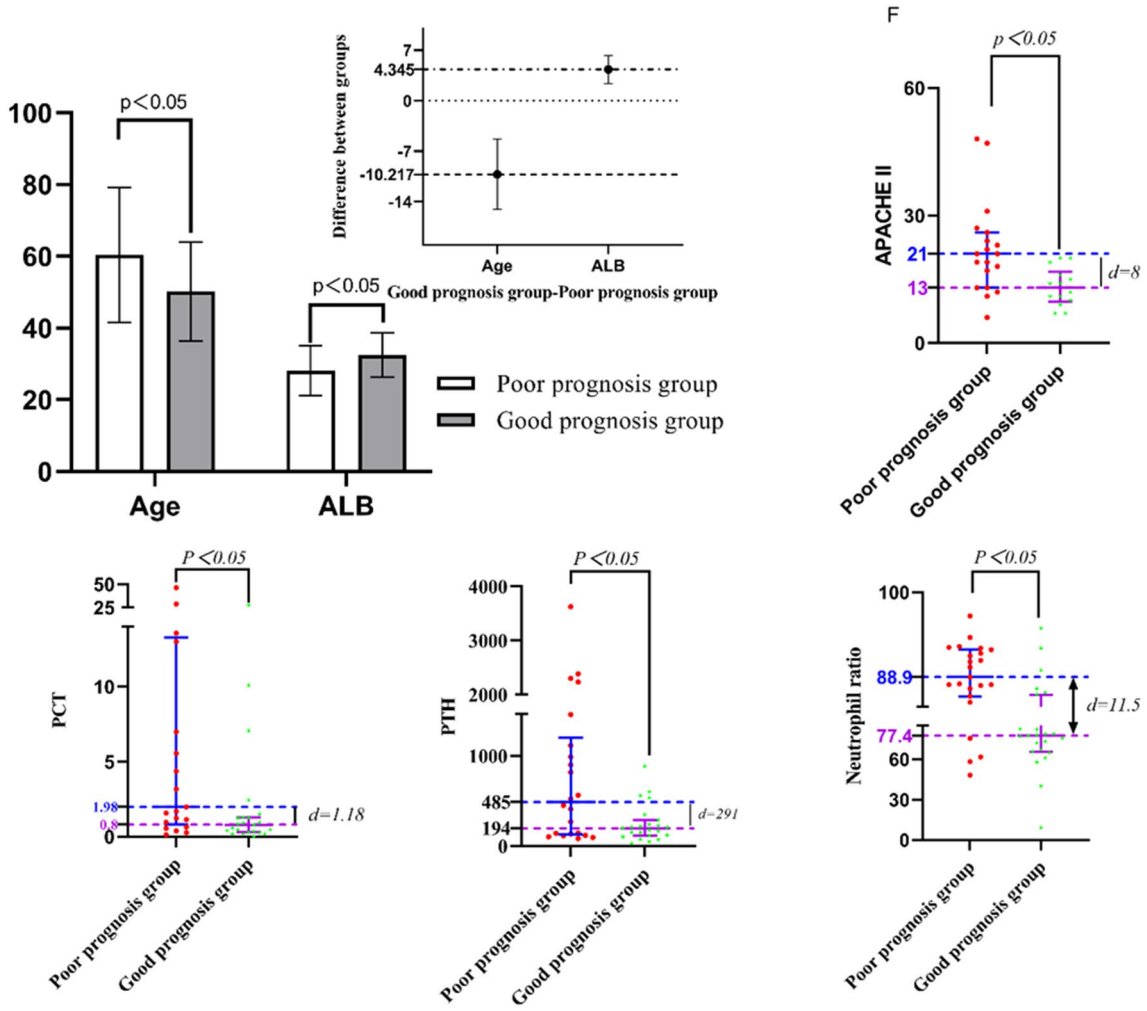

Fig. 1 Differences in clinical indicators between the poor prognosis group and the good prognosis group

Table 2 Results of binary logistic regression analysis for prognosis of severe SHPT patients in ICU

Variables				95% confidence interval of EXP (B)		
	B	Standard Error	Sig	Exp (B)	Lower limit	Upper limit
Age	0.073	0.032	0.022	1.076	1.011	1.145
PTH	0.004	0.002	0.03	1.004	1	1.007
WBC	0.259	0.119	0.029	1.295	1.026	1.634
ALB	-0.22	0.111	0.048	0.803	0.645	0.998

index were calculated for each indicator. The AUC of age, admission PTH, WBC, ALB, and neutrophil ratio were 0.687 (95% CI 0.529–0.844), 0.682 (95% CI 0.518–0.846), 0.771 (95% CI 0.629–0.912), and 0.764 (95% CI 0.613–0.914), respectively, which were greater than 0.5, demonstrating the predictive value of the screened clinical indicators. The AUC of ROC that combined age, admission PTH, WBC, ALB, and neutrophil ratio together to predict prognosis was 0.889 (95% CI 0.796–0.983), and the AUC was greater than 0.8.This combined prediction model had good predictive value. (Table 3, Fig. 2).

4 Discussion

The prevalence of CKD has been increasing in recent years. The global prevalence of CKD was approximately 9.1% in 2017, and more than 1.2 million people died from chronic

Table 3 AUC, sensitivity, specificity and maximum Youden index bound for each index of ICU critical care SHPT in predicting prognosis

Indicators	AUC	Sig	95% CI		Sensitivity (%)	Specificity (%)	Maximum Youden index bound
			Lower limit	Upper limit			
Age	0.687	0.032	0.529	0.844	86.96	52.17	51
PTH	0.682	0.037	0.518	0.846	59.09	82.61	346
WBC	0.771	0.002	0.629	0.912	56.52	91.30	11.95
Neutrophil ratio	0.764	0.002	0.613	0.914	82.61	73.91	82.4

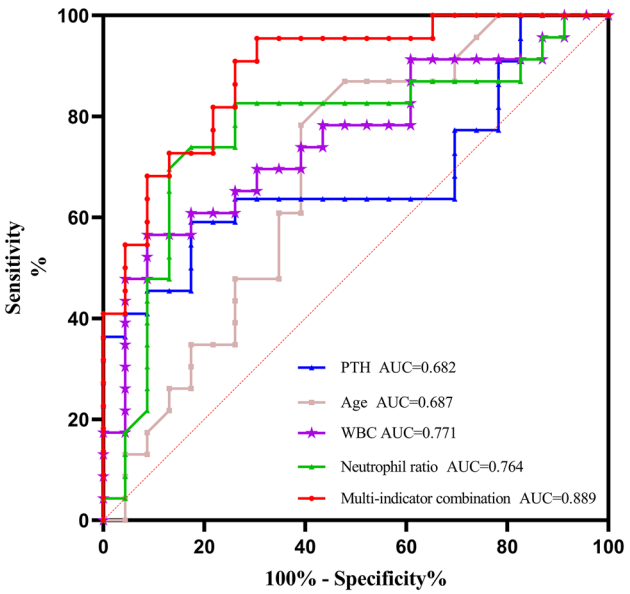

Fig. 2 ROC curves of ICU admission indicators for critically ill SHPT patients in predicting the poor prognosis

kidney disease and its related disorders in 2017 alone [13]. Secondary hyperparathyroidism is one of the most common complications of CKD and has a very high rate of morbidity and mortality [14]. With continuous advances in dialysis technology, the survival of patients with CKD has been significantly improved. The incidence of SHPT has gradually increased with the increase in dialysis duration. The main causes of poor prognosis in this study were cardiovascular events (47.8%) and sepsis (39.2%), which may be associated with higher PTH levels and poor nutritional status in severe SHPT. PTH is currently considered to be one of the toxins in CKD. Quality of life guidelines for patients with kidney disease set parathyroid hormone targets for dialysis patients at 2–9 times normal values [15]; however, too wide target intervals make it difficult to make a valid assessment of the prognosis of patients with SHPT. It has been reported that high levels of PTH are closely associated with vascular calcification and that PTH levels are independent risk factors for high coronary artery calcification scores in CKD dialysis patients [16, 17]. In turn, vascular calcification can directly increase cardiovascular mortality in CKD patients. When pharmacological or surgical intervention is performed early in the onset of SHPT patients to control PTH levels, the level of vascular calcification decreased and there was a significant improvement in arterial wall and myocardial fibrosis [18, 19], which demonstrates, to some extent, the significance of controlling PTH on the incidence of cardiovascular events in SHPT patients. In addition to its effects on the cardiovascular system, the role of PTH in inflammatory stress and sepsis has also received attention from researchers in recent years. The chronic high PTH state in SHPT patients leads to further disorders of calcium and phosphorus metabolism and resistance to PTH in target organs such as the kidney and bone. In sepsis, hypocalcemia is an independent risk factor for poor prognosis [20], and the loss of PTH, an important hormone that regulates calcium and phosphorus metabolism in the body, will have a detrimental effect on patients. And it has been confirmed in animal experiments that moderately high PTH is associated with poor prognosis in sepsis [21, 22], which is consistent with the findings in our study. In a follow-up study, the incidence of adverse events in patients with SHPT was found to be significantly lower in the PTH range of 150 to 300 ng/mL than in the high level group [8]. Chronically high levels of PTH are characteristic of SHPT, and high levels of PTH increase the risk of vascular and valvular calcification and cause ventricular remodeling. Using a cutoff value of 300 ng/L, the subjects in this study were divided into high and low PTH groups, and the probability of adverse prognosis was found to be significantly lower in the low PTH group than in the high PTH group (35.7% < 72.2%, $P < 0.05$). The risk of adverse prognosis was 5.2 (95% CI 1.41–19.18, $P < 0.05$) times higher in the high PTH group than in the low PTH group. PTH was an independent risk factor for adverse prognosis in severe SHPT.

The prognosis of SHPT patients with low albumin levels was observed to be relatively poor in this study. As the predominant protein in human plasma, albumin assumes a variety of physiological functions and has a very important role in the human body, and is also often used as an indicator to evaluate the nutritional status of patients. Studies have shown that low human blood albumin levels are closely

associated with ischemic heart disease, heart failure, atrial fibrillation, stroke and other cardiovascular and cerebrovascular events [23–25]. During the development of sepsis, the body is in a state of stress, with elevated body temperature, increased consumption, accelerated albumin metabolism and rapid depletion of albumin in the body, while infection affects capillary permeability, causing a large amount of intravascular albumin to leak out via capillaries and a rapid decrease in serum albumin levels [26]. Hypoalbuminemia is closely related to systemic inflammatory storm and organ failure [27]. Current domestic and international studies have concluded that hypoalbuminemia is an independent risk factor for severe sepsis [28, 29]. Considering that the causes of poor prognostic events in this study were mostly cardiovascular events and sepsis, we speculated that serum albumin levels had a role in assessing the prognosis of severe SHPT. In the follow-up study, albumin was found as an independent protective factor for severe SHPT, the prognosis of the high albumin group was better than that of the low albumin group (56.5% > 43.5% $P < 0.01$). This, to some extent, validated our earlier speculations and demonstrated the value of proving albumin in assessing the prognosis of patients with severe SHPT.

The results of this study showed that leukocytes were an independent risk factor for severe SHPT. The admission leukocyte count was higher in the poor prognosis group than in the good prognosis group, and the difference was statistically significant. Leukocytosis is commonly used to diagnose infectious diseases [30] and is a routine test for almost every patient admitted to the hospital. However, because of the effect of stress on the leukocyte count when the organism is stimulated by factors such as acute inflammation, leukocytes in peripheral blood increase or decrease when bone marrow hematopoiesis is increased or suppressed by toxicity, which may lead to normal or increased leukocytes in sepsis. Therefore, its value as an indicator of infection is low and lacks sufficient specificity [31]. In the present study, the predictive value of WBC on admission using ROC curves was evaluated with the opposite result. The AUC of the ROC curve for WBC at admission in patients with severe SHPT was 0.771, with a maximum Youden index cut-off of 11.95 × 10^9/L, at which point the sensitivity was 56.52% and the specificity was 91.30%. The entry WBC index has a better predictive value, higher specificity and lower sensitivity for poor prognosis in patients with severe SHPT compared with other indexes, which may be related to bone marrow hematopoietic tolerance and compensation due to long-term chronic inflammation and renal-type anemia in patients with severe SHPT.

Age as an independent risk factor for cardiovascular events and sepsis has been clearly reported in national and international studies [32–34]. And in the present study cardiovascular events and sepsis were the major causes of death in severe SHPT. In the present study, there was a significant difference (86.9% > 52.1%, $P < 0.01$) in mortality between the older group (≥ 50 years) and the younger group (< 50 years), and the risk of adverse prognosis in the older group was 6.1(95% CI 1.4–26.4) times higher than the younger group, using 50 years as the cut-off value. The results of this study show that age is also an independent risk factor for poor prognosis in severe SHPT.

The present study has some limitations. First, this is a retrospective study, and based on the characteristics of retrospective studies, the strength of proof of causality is limited. In addition, this study is a single-center study with a relatively small sample size. A multi-center, large sample size study is needed to further validate the results of this study. Moreover, the clinical indicators covered in this study are few and may be insufficient to fully assess the severity of secondary hyperparathyroidism. In the next step, we will incorporate other relevant indicators such as parathyroid ultrasound, coronary artery calcification score and SOFA score to assess the severity of disease and risk of the poor prognosis in patients with severe secondary hyperparathyroidism.

5 Conclusion

In conclusion, cardiovascular events and sepsis are the main causes of poor prognosis in severe SHPT. Age, PTH, and WBC are independent risk factors for poor prognosis of severe SHPT, and ALB is an independent protective factor for poor prognosis. For patients with severe SHPT, the risk of the poor prognosis should be assessed as early as possible based on age, admission PTH, WBC, ALB, and neutrophil ratio to enhance the identification of high-risk patients. These information may help to actively control PTH levels, reduce the degree of systemic inflammation, ensure balanced nutritional intake, and increase patients' serum albumin levels to improve their prognosis.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s44231-022-00025-0.

Acknowledgements Not applicable.

Authors'contribution Wenhao Duan, Shouhua Zheng contributed to the study conception and design. Wenhao Duan, Ying Yan gathered the data. Wenhao Duan performed the data analysis and interpretation. Ying Yan and Xiaonuo Shi revised the manuscript. Shouhua Zheng gave final approval of the version to be published. All authors read and approved the final manuscript.

Funding This work was supported by Henan Province Medical Science and Technology Research: SBGJ2018026.

Availability of supporting data Not applicable.

Declarations

Conflict of interest The authors declare no conflicts of interest.

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