Predictive value of thyroid hormone levels in adverse prognosis in patients with newly diagnosed multiple myeloma

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Abstract

Background: The level of thyroid hormones (TH) influences the prognosis of a wide range of diseases. Despite this, to date, there have been few studies that have evaluated the effect of TH levels on the prognosis of patients with multiple myeloma (MM). As a result, we investigated the effect of TH levels on survival in patients with MM.

Methods: TH levels and common adverse prognostic markers were compared in 124 newly diagnosed MM patients. To evaluate differences between categorical and continuous variables, Chi-Square test and Fisher's Exact test as well as Mann-Whitney U test were used. Kaplan-Meier test was used for survival analysis, and Cox proportional risk regression was used for univariate and multivariate analysis of overall survival (OS).

Results: A significant decrease in total thyroxine (TT4) and total triiodothyronine (TT3) was observed in patients with multiple myeloma (P <0.05) compared to healthy subjects. In multiple myeloma patients, the levels of TT4, TT3, free (F)T4, and FT3 in non-survivors were significantly lower than those in survivors (P <0.05), and TT4 levels were significantly positively correlated with hemoglobin and albumin levels (P <0.05). The Cox proportional hazard model revealed that age≥68 years (HR=0.463, 95%CI =0.226-0.900, P=0.036) and TT4≤67.66 nmol/L (HR=0.204, 95%CI=0.101-0.412, P <0.001) were an independent prognostic factors for OS in multiple myeloma patients (P <0.05).

Conclusions: Thyroid hormone levels, particularly TT4, may be an important predictor of poor prognosis in patients with MM.

Introduction

Multiple myeloma (MM) is a B-cell proliferative malignancy of the bone marrow that accounts for 1% of all cancers and is the second most common hematological malignancy after lymphoma [1]. A characteristic feature of MM is the clonal proliferation of malignant plasma cells, which can result in hematological dysfunction, osteolytic disorders, hypercalcemia, and renal failure [2]. The development of immunomodulators and proteasome inhibitors enhances survival as treatment advances [3]. However, MM is still incurable and has frequent relapses that are related to many factors. Therefore, correctly identifying specific risk factors associated with MM remains a critical issue. MM mainly occurs in middle-aged and elderly people. Elderly patients are a highly diverse group, and the clinical course of MM patients is quite variable due to this diverse set, which makes the prognostic factors of MM complicated and diversified. Earlier reported risk factors for adverse prognosis include old age, low hemoglobin level, high marrow plasma cell ratio, hypercalcemia, and so on [4-7]. With the development of detection indicators, prognostic indicators for myeloma evaluation are constantly being updated. Complement 4 was found to be related to the clinical prognosis of MM patients [8]. Serum B-cell Antigen (sBCMA) was demonstrated to be associated with plasma cells in bone marrow, suggesting that it could be used as a novel independent marker to monitor and predict the prognosis of MM patients [9]. An increasing number of prognostic markers have been discovered for MM, which inspires us to seek novel prognostic indicators from various perspectives to assess the prognosis of MM in an elaborately and more accurately, which can help assess the stage and spread of the disease and its prognostic path.

Thyroid function serves as a command center for physiological and pathological processes. Thyroid hormone (TH) regulates and coordinates the fundamental physiological processes of appropriate development, growth, and energy metabolism, and thus, it plays an important function in various processes [10]. Serum TH levels fluctuate in severe disorders, the most prevalent of which is low triiodothyronine (T3) syndrome, also known as non-thyroid disease syndrome or morpheus thyroidism syndrome, which is defined by low free T3 (FT3) levels in the blood. This is accompanied by normal to low serum free thyroxine (FT4) and thyroxine stimulating hormone (TSH) levels [11]. Low TH negatively interacts with various hemodynamic parameters; it is associated with poor prognosis of acute severe and

long-term non-thyroid illnesses and is considered to exacerbate cardiac remodeling and progression of heart failure [12]. TH replacement therapy is safe and can improve hemodynamic function in patients with heart failure [13]. TH may also be utilized to predict short- and long-term mortality in pulmonary infection, elderly hospitalized patients, and any non-critical patients [14-16]. TH level were recently found to be significantly correlated with the risk of cancer (such as prostate cancer, melanoma, uterine cancer, lung cancer) [17]. These studies suggest that changes in TH levels may be correlated with the severity and prognosis of various diseases.

A number of factors contribute to the occurrence and development of multiple myeloma, including hematopoietic dysfunction, complex gene polymorphism, immune dysfunction, coagulation dysfunction, tissue damage, and other complications [18], all of which can affect and interfere with thyroid gland functions indirectly. Studies have found that hormonal and endocrine imbalances occur in MM patients [19]. However, research on the effect of TH on the prognosis of patients with multiple myeloma is limited. To evaluate thyroid function in patients with MM and determine the relationship between TH levels and known prognostic factors of multiple myeloma disease, disease stage, and survival, we reviewed thyroid levels of 124 MM patients at admission along with prognostic estimated of common myeloma.

Methods

Patients and healthy controls

One hundred and twenty-four newly diagnosed MM patients from the Hematology Department of The First People's Hospital of Yunnan Province were studied retrospectively, as per the following inclusion criteria: 1) newly diagnosed MM patients in accordance with the International Myeloma Working Group diagnostic criteria [20], 2) no special medication history, 3) no history of other tumors, thyroid disease or any chronic diseases. Patients included received chemotherapy alone. Excluded patients were those followed by hematopoietic stem cell transplantation and other specialized treatments. The enrolled patients had their first visit between July 1, 2015, to January 1, 2019 and were followed up for two years. Fifty-two healthy individuals who were age, gender, and race matched were included as controls. At the time of diagnosis, patient medical records, laboratory results, and clinical characteristics of all patients were obtained Patients were followed up by phone or by reviewing their medical records, and the results were recorded at the hospital.

A number of clinical parameters were recorded including age, gender, diagnostic typing, the Durie-Salmon (DS) staging system, the bone marrow plasma cells percentage, β2-microglobulin (β2MG), hemoglobin (HB), albumin, globulin, blood urea nitrogen (BUN), creatinine (Cr), calcium, TSH, total thyroxine (TT4), total triiodothyronine (TT3), FT4, FT3, date of initial treatment, survival status, date of death or date of the last follow-up. This study was approved by the Ethics Committee of The First People's Hospital of Yunnan Province (KHLL2022-KY024) and was conducted in strict accordance with the principles of the Declaration of Helsinki and the International Ethical Guidelines for Biomedical Research Involving Humans jointly formulated by the World Health Organization. All subjects provided written informed consent.

Statistical Analyses

A primary endpoint of follow-up was overall survival (OS), defined as the time during follow-up for diagnosis to death or the date of the last follow-up. Categorical variables are represented by frequency and percentage (n, %), and continuous variables by median and quartile range (IQR). In cases where categorical values were compared or binary variables were compared, the Chi-square test or Fisher’s exact test was used, while in cases where continuous variables were compared, the Mann-Whitney U test was used. Pearson test was used to analyze the correlation between

continuous variables. Receiver Operating Characteristics Curve (ROC) was prepared to determine the optimal cut-off value for predicting the survival of various variables. For survival analysis, the Kaplan-Meier method was utilized, and to determine the statistical significance of differences between the curves, the log-rank test was performed. For univariate and multivariate analysis, Cox proportional risk models were used to determine independent prognostic factors for OS. P <0.05 on both sides was considered statistically significant. IBM SPSS 21.0 software package (SPSS, USA) was used for statistical analysis, and GraphPad Prism7 software was used for plotting.

Results

Baseline characteristics

Thyroid function indexes of patients with MM and healthy subjects are shown in Table 1 and Figure 1. Compared of healthy individuals, newly diagnosed patients with MM had significantly increased TSH levels (P < 0.05), and significantly decreased TT4, TT3, and FT3 levels (P < 0.05) (Table 1). The clinical characteristics of all patients at diagnosis are listed in Table 1. A total of 124 patients met inclusion criteria (73 males and 51 females), with a median age of 58 years (IQR: 53-64 years). According to the DS staging system, 18 patients (14.5%) were stage II and 106 (85.5%) were stage III MM. The median survival of enrolled patients was 749 days (IQR 353-1059). The median clinical parameters of all patients were: plasma cells ratio = 34%, β2MG = 6.22 mg/L, TSH = 2.46 mIU/L, TT4 = 82.49 nmol/L, TT3=1.36 nmol/L, FT4=14.72 pmol/L, FT3 = 3.94 pmol/L, HB = 85 g/L, albumin = 33 g/L, globulin = 60 g/L, BUN = 6.2 mmol/L, Cr = 88 umol/L, and calcium = 2.24 mmol/L (Table 1).

Comparison of clinical indicators between survivors and non-survivors

All MM patients were divided into two broad categories namely, survivors (n = 69,55.6%) and non-survivors (n = 55,44.4%) based on whether they survived within 2 years of diagnosis. The clinical indicators of the two groups were compared, and the results are shown in Table 1 and Figure 1. Non-survivors had considerably lower median survival than survivors (275 vs 975 days, P < 0.001). The proportion of survivors diagnosed with Durie-Salmon Stage III was significantly lower than that of non-survivors (78.3% vs 94.5%, P = 0.019). Compared with survivors, non-survivors were older, had a higher proportion of marrow plasma cells, and had higher serum β2MG and Cr levels. The levels of hemoglobin and albumin were significantly decreased in non survivors (P = 0.020, P = 0.033, P = 0.034, P = 0.030, P = 0.001 and P = 0.003 respectively). Comparison of thyroid function indexes showed that non-survivors had significantly lower TT4, TT3, FT4, and FT3 levels than survivors (71.10 vs 92.57 nmol/L, P < 0.001; 1.17 vs 1.50 nmol/L, P < 0.001; 13.60 vs 15.09 pmol/L, P = 0.005; 3.47 vs 4.21 pmol/L respectively, P = 0.001) (Table 1 and Figure 1). There were no statistically significant differences between the two groups in terms of gender, globulin, BUN, calcium and TSH levels.

The Cutoff-value of cytokines between survivors and non-survivors

The optimal cutoff-value for predicting the prognosis of patients were determined and early risk factors suggesting poor prognosis of MM patients were explored. Cutoff value was determined by ROC curve and the results are shown in Table S1. The cutoff-value of each indicator was: age = 68 years (95% CI=0.486-0.719, P = 0.007), plasma cells = 30.75% (95% CI=0.541-0.766, P = 0.039), β2MG = 6.63 mg/L (95% CI= 0.543-0.767, P = 0.010), HB = 82 g/L (95% CI=0.588-0.783, P = 0.001), albumin = 28 g/L (95% CI=0.576-0.744, P = 0.001), globulin 73.5 g/L (95% CI=0.509-0.738, P = 0.041), BUN = 6.25 mmol/L (95% CI=0.478-0.714, P = 0.202), Cr = 93 μmol/L (95% CI=0.496-0.736, P = 0.031), calcium = 2.07 mmol/L (95% CI = 0.391-0.618, P = 0.937), TSH = 1.58 mIU/L (95% CI=0.465-0.678, P = 0.192), TT4 = 67.66 nmol/L (95% CI=0.621-0.815, P = 0.001), TT3 = 1.25 nmol/L (95% CI = 0.551-0.759, P = 0.004), FT4 = 14.06 pmol/L (95% CI=0.495-0.723, P = 0.045), FT3 = 3.27 pmol/L (95% CI = 0.579-0.783, P = 0.001).

Univariate and multivariate analyses of prognosis factors for OS

To determine the impact of each statistically significant clinical indicator determined by the ROC curve on survival, Kaplan-Meier, univariate, and multivariate analyses were used. The results are shown in Table 2, Figure 2, and Figure S1. In the univariate analysis, age ≥68 years (HR = 0.297, 95% CI = 0.167-0.530, P = 0.001), DS stage Ⅲ (HR = 3.549, 95% CI =1.108-11.37, P = 0.033), plasma cell ≥30.75% (HR = 0.438, 95% CI = 0.241 0.796, P = 0.007), plasma cell ≥30.75% (HR = 0.438, 95% CI = 0.241-0.796, P = 0.007),β2MG ≥6.63 mg/L (HR = 2.178, 95% CI = 1.161-4.084, P = 0.015), HB ≤82 g/L (HR = 0.406, 95% CI = 0.233-0.710, P = 0.002), albumin ≤28 g/L (HR = 0.386, 95% CI = 0.226-0.659, P = 0.001), globulin ≥73.5 g/L (HR = 1.848, 95% CI = 1.076-3.173, P = 0.026), Cr ≥93 μmol/L (HR = 2.346, 95% CI = 1.348-4.082, P = 0.003), TT4 ≤67.66 nmol/L (HR = 0.233, 95% CI = 0.130-0.383, P = 0.001), TT3 ≤1.58 nmol/L (HR = 0.354, 95% CI = 0.207-0.607, P = 0.002), FT4 ≤14.06 pmol/L (HR=0.435, 95% CI=0.251-0.755, P=0.003), FT3≤3.27 pmol/L (HR = 0.271, 95% CI=0.159-0.462, P=0.003) were significantly associated with 2-year OS. In addition, the survival curve of MM patients based on the Kaplan-Meier method also revealed risk factors consistent with the results of univariate analysis (Figure 2A-B and Supplementary Figure S1, A-H). Multivariate regression analysis was then performed to investigate independent predictors of adverse outcomes in MM patients. Age ≥68 years (HR = 0.463, 95% CI = 0.226-0.900, P = 0.036) and TT4 ≤67.66 nmol/L (HR = 0.204, 95% CI = 0.101-0.412, P <0.001) can be an independent prognostic factor for OS in patients with MM (Table 2).

Clinical characteristics of patients with different levels in TT4

The results of the comparison of clinical characteristics of MM patients with different TT4 levels revealed that patients with higher TT4 levels had a longer survival time (808 vs 368 days, P < 0.001), lower β2MG levels (5.35 vs 9.32 mg/L, P = 0.016), higher HB levels (91 vs 74 g/L, P = 0.001), higher albumin levels (33 vs 28 g/L, P = 0.007), higher TT3 levels (1.47 vs 0.97 nmol/L, P <0.001), higher FT4 levels (15.85 vs 13.39 pmol/L, P < 0.001), and higher FT3 levels (4.14 vs 4.14 pmol/L, P < 0.001) (Table 3). However, there were no significant differences in age, plasma cells ratio, globulin, BUN, Cr, calcium, and TSH levels between the two groups.

Correlation analysis of TT4 level and other clinical indicators in patients with multiple myeloma

Correlation analysis was conducted between significant clinical indicators in different TT4 levels with different TT4 levels (Table 4). The results showed that FT4 (r= 0.729, P < 0.001), HB (r = 0.251, P = 0.005) and albumin (r = 0.350, P < 0.001) levels were positively correlated with TT4 levels. However, β2MG (r = -0.165, P = 0.099), TT3 (r = -0.131, P = 0.145) and FT3 (r = 0.071, P = 0.435) levels were not significantly correlated with TT4 levels.

Discussion

The results from the present study indicated that TT4 and TT3 levels were considerably lower in patients with MM than in healthy individuals. TT4, TT3, FT4, and FT3 levels of MM patients were considerably lower in non-survivors than in survivors. TT4 levels were significantly positively correlated with HB and albumin levels. Advanced age and low TT4 level were independent prognostic factors for OS in these patients, suggesting that endocrine system disorders had a significant impact on the survival of patients with MM.

TH parameters mainly include TSH, TT3, TT4, FT4, and FT3. Among them, TT3 and TT4 have mainly protein binding roles in circulation, and are in equilibrium with the bioactive FT4 and FT3. The production and secretion of TH is a tightly regulated process governed by classical negative feedback mechanism involving the thalamus, pituitary, and thyroid, through a well-known hypothalamic-pituitary-thyroid axis, which together maintain normal physiological levels of TH. The normal reference ranges of TH levels in Chinese population are TSH = 0.71-4.92 mIU/L, FT4 = 12.2-20.1 pmol/L, FT3= 3.9-6.0 pmol /L, TT4 = 65.6-135.1 nmol/L, and TT3 = 1.2-2.2 nmol/L [21]. In our study, univariate analysis showed that TT4 ≤67.66 nmol/L, TT3 ≤1.58 nmol/L, FT4 ≤14.06 pmol/L, and FT3 ≤3.27 pmol/L were significantly

correlated with poor prognosis in patients with MM. In addition, TT4 ≤67.66 nmol/L was still an independent prognostic factor of OS in multivariate analysis, indicating that TH levels were reduced in MM patients and also affected the prognosis of MM.

TH is required for tissue maturation and general health. It is involved in regulating growth, development, and key metabolic pathways, including glucose, cholesterol, and fatty acid metabolism in different tissues [22, 23]. In addition, it can increase oxygen consumption and ATP hydrolysis and reduce the coupling state of mitochondria, resulting in the catabolism of all types of energy sources [24]. Endocrine and immune systems are intricately complex and interconnected; TH play an important role in the regulation of specific immune response through a variety of mechanisms, which can affect the participation of immune cells in the regulation of immunity, and mediate cellular immunity, natural killer cell activity and proliferation of T and B lymphocytes [25-27]. TH metabolism affects a variety of tissues and cells, therefore, changes in circulating TH levels may lead to an improvement or worsen deterioration of the clinical situation. The significant association between TH and several clinical diseases has been demonstrated in previous studies. For example, TH function is significantly correlated with deterioration of cardiovascular status, and low TH levels increased the mortality due to heart failure [13]. TH can enhance heart rate and cardiac contractility, improve cardiac systolic and diastolic functions, and reduce vascular resistance [14]. Additionally, thyroid dysfunction has also been found in patients with diabetes, aging, and a variety of tumors [28], indicating the complex molecular mechanism of the TH regulation system, which may influence the occurrence and progression of diseases by different systems and tissues.

In the present study, TT4 levels in patients with MM were significantly positively correlated with albumin and HB levels, which was congruent with previous findings [29, 30]. This implies that for chronic hematological malignancies, TH may affect the physiology and pathology of the blood system through different mechanisms, and TH and disease may interact with each other through multiple factors, including the immune system, malnutrition, and hematopoietic system. TH plays a pivotal role in regulating hematopoiesis through the Krüppel-like factor 9 (KLF9) axis [31]. Thyroid dysfunction can adversely affect all blood parameters except platelets [32]. It stimulates erythropoiesis in the bone marrow independently of renal or extrarenal production of erythropoietin (Epo) and directly affects erythrocyte progenitor cell proliferation and stimulates erythropoiesis in the bone marrow. [33, 34]. TH also stimulates erythropoiesis by inducing the expression of Epo mRNA and protein [31, 35]. Low TH levels can predict the occurrence of anemia [36]. In addition, TH disorder impairs immune function, destroys coagulation balance, and leads to cardiac dysfunction and respiratory dysfunction [37]. Significant hypothyroidism leads to an increased risk of bleeding complications, while hyperthyroidism is associated with venous thromboembolism; fT4 levels are associated with elevated levels of factor VII, fibrinogen, and Von Willebrand factor [38]. T4 levels also seem to promote platelet aggregation and degranulation, while T3 levels seem to have no effect on platelets [39]. Research is still needed to determine the pathophysiological mechanisms involved in the interaction between TH and the blood system.

The present study has some limitations. First, this study was a retrospective study of a single research center, and comprehensive factors were not considered. Second, a limited number of patients were enrolled in the study Third, patient genetic information was omitted. Lastly, the included data are TH levels at a single time point, and changes in TH levels over time were not considered. Therefore, further studies are needed to confirm these findings and elucidate the role of TH levels in MM progression and survival.

Conclusions

To conclude, the present study found that the levels of THs (TT4, TT3, and FT3) were significantly lower in patients with MM than in healthy individuals In multiple myeloma patients, the levels of TT4, TT3, FT4, and FT3 in non-survivors were considerably lower than those in survivors. Low TT4 levels can be an independent prognostic factor for OS in

patients with MM and TT4 levels are significantly positively correlated with HB and albumin levels. The findings indicate abnormal functioning of the endocrine system in patients with MM and TH levels has a significant impact on their survival. This study also implies that TH replacement therapy may improve the prognosis of patients with MM and having low TH levels. Furthermore, the convenience and wide application of serum TH detection make it easier to evaluate the prognosis of patients with MM. Future large-scale, multi-center prospective studies will further clarify the role and mechanism of TH in influencing the prognosis of MM.

Declarations

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Declaration of conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Authors' contributions

LZ, ZL and HH performed the research and wrote the paper. XL and FL contributed clinical data. All authors listed have made a substantial, direct, and intellectual contribution to the work and approved it for publication.

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Ethical Approval and Consent to participate

The study was carried out in strict compliance with the Declaration of Helsinki and was also approved by the Ethics Committee of the First People's Hospital of Yunnan Province (KHLL2022-KY024).

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors without undue reservation.

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Tables

Table 1. Demographic, clinical, and laboratory data of survival and non-survival of multiple myeloma patients on admission.

Variables	Control group	Total (n=124)	Survivors (n =69)	Non-survivors(n =55)	P value
Age, years	40(34-56)	58(53-64)	57(52-63)	64(55-68)	0.020
Sex (male/female)	23/29	73/51	43/26	30/25	0.382
TSH(mIU/L)	2.07(1.49-2.68) #**	2.46(1.87-4.77)	2.46(1.87-5.06)	2.74(1.68-4.34)	0.121
TT4(nmol/L)	96.3(80.98-17.80) #**	82.49(66.27-103.27)	92.57(79.16-106.30)	67.10(56.43-89.49)	<0.001
TT3(nmol/L)	2.58(1.47-1.82) #***	1.36(1.06-1.74)	1.50(1.25-1.80)	1.17(0.92-1.51)	<0.001
FT4(pmol/L)	15.49(14.03-17.35) #ns	14.72(13.41-16.89)	15.09(14.26-16.89)	13.60(11.45-17.07)	0.005
FT3(pmol/L)	4.28(3.99-4.78) #***	3.94(3.16-4.36)	4.21(3.39-4.57)	3.47(2.69-4.09)	0.001
survival time(days)	—	749(353-1059)	975(760-1345)	275(133-455)	<0.001
DS stage(/)	—	18/106(14.5%/85.5%)	15/54(21.7%/78.3%)	3/52(5.5%/94.5%)	0.019
Treatment regimens	—				ns
Bortezomib-based therapies	—	100(80.6%)	55(79.7%)	45(81.8%)	
Thalidomide-based therapies	—	24(19.4%)	14(20.3%)	10(18.2%)	
Plasma cells(%)	—	34(21-50)	29.5(19.5-42.75)	37.5(25.8-55.5)	0.033
β2MG(mg/L)	—	6.22(3.29-11.6)	5.35(2.86-10.35)	8.56(3.51-16.96)	0.034
HB(g/L)	—	85(71-105)	96(76-110)	77(66-92)	0.001
Albumin(g/L)	—	33(25-37)	34(28-39)	28(24-34)	0.003
Globulin(g/L)	—	60(34-78)	54(29-74)	66(36-84)	0.057
BUN(mmol/L)	—	6.2(4.8-9.5)	6.0(4.8-8.2)	6.7(5.3-12.3)	0.073
Cr (umol/L)	—	88(74-174)	81(73.5-121.0)	111.5(74.0-235.8)	0.030
Calcium(mmol/L)	—	2.24(2.06-2.49)	2.24(2.10-2.46)	2.24(2.03-2.57)	0.983

Categorical variables were represented by n(%), and continuous variables were represented by median and quartile range (IQR).

Comparison of thyroid function-related indicators between multiple myeloma(MM) patients and control group, ** P < 0.01; ***P < 0.001; ns, not significant.

Abbreviations: DS, Durie-Salmon staging system;β2MG, β2-microglobulin;

TSH ,Thyroid stimulating hormone;TT4,Total thyroxine; TT3,Total triiodothyronine; FT4 , Free thyroxine ;FT3 ,Free triiodothyronine;HB, Hemoglobin; BUN,Blood Urea Nitrogen; Cr,Creatinine;ns,not significant.

Table 2. Univariate & multivariate analysis of prognostic factors for overall survival (OS) in the study population (n = 124).

	Univariable analysis		Multivariable analysis	
Variable	HR(95%CI)	P value	HR(95%CI)	P value
Age≥68 years	0.297(0.167-0.530)	0.001	0.463(0.226-0.900)	0.036
DS stage □	3.549(1.108-11.37)	0.033		
Plasma cell≥30.75%	0.438(0.241-0.796)	0.007		
β2MG≥6.63mg/L	2.178(1.161-4.084)	0.015		
HB≤82g/L	0.406(0.233-0.710)	0.002		
Albumin≤28 g/L	0.386(0.226-0.659)	0.001		
Globulin≥73.5g/L	1.848(1.076-3.173)	0.026		
Cr≥93 umol/L	2.346(1.348-4.082)	0.003		
TT4≤67.66nmol/L	0.233(0.130-0.383)	0.001	0.204(0.101-0.412)	<0.001
TT3≤1.58 nmol/L	0.354(0.207-0.607)	0.002		
FT4≤14.06 pmol/L	0.435(0.251-0.755)	0.003		
FT3≤3.27 pmol/L	0.271(0.159-0.462)	0.003		

Through multivariate analysis of risk factors, significantly different ages and level of TT4 and HB was observed in survivors and non-survivors with a hazard ratio of 1.443, 0.246 and 0.767, respectively.

Abbreviations: HR hazard ratio, CI confidence interval.

Table 3. Comparison of serum parameters among patients with different TT4 levels.

Variable	TT4>67.66 nmol/L(n=90)	TT4≤67.66 nmol/L(n=34)	P value
Age, years	58(23-63)	60(55-68)	ns
survival time(days)	808(650-1189)	368(173-651)	<0.001
Plasma cells(%)	33.5(21.0-47.6)	36.0(19.1-53.1)	ns
β2MG(mg/L)	5.35(2.82-10.4)	9.32(4.63-18.16)	0.016
HB(g/L)	91(76-108)	74(61-90)	0.001
Albumin(g/L)	33(27-38)	28(24-34)	0.007
Globulin(g/L)	58(29-75)	64(36-93)	ns
BUN(mmol/L)	6.05(4.80-8.25)	7.7(5.05-14.05)	ns
Cr (umol/L)	83(71-134)	120(85.5-237.5)	ns
Calcium(mmol/L)	2.25(2.09-2.45)	2.20(2.03-2.72)	ns
TSH(mIU/L)	2.46(1.87-4.83)	3.86(1.98-4.34)	ns
TT3(nmol/L)	1.47(1.25-1.75)	0.97(0.86-1.16)	<0.001
FT4(pmol/L)	15.85(14.26-17.74)	13.39(10.02-13.68)	<0.001
FT3(pmol/L)	4.14(3.41-4.56)	2.78(2.06-3.58)	<0.001

Categorical variables were represented by n(%), and continuous variables were represented by median and quartile range (IQR); ns, not significant (P>0.05).

Table 4. Correlation of TT4 with other clinical indicators among MM patients.

Parameters	Correlation coefficient	P value
β2MG	-0.165	0.099
TT3	-0.131	0.145
FT4	0.729	<0.001
FT3	0.071	0.435
HB	0.251	0.005
Albumin	0.350	<0.001

Figures

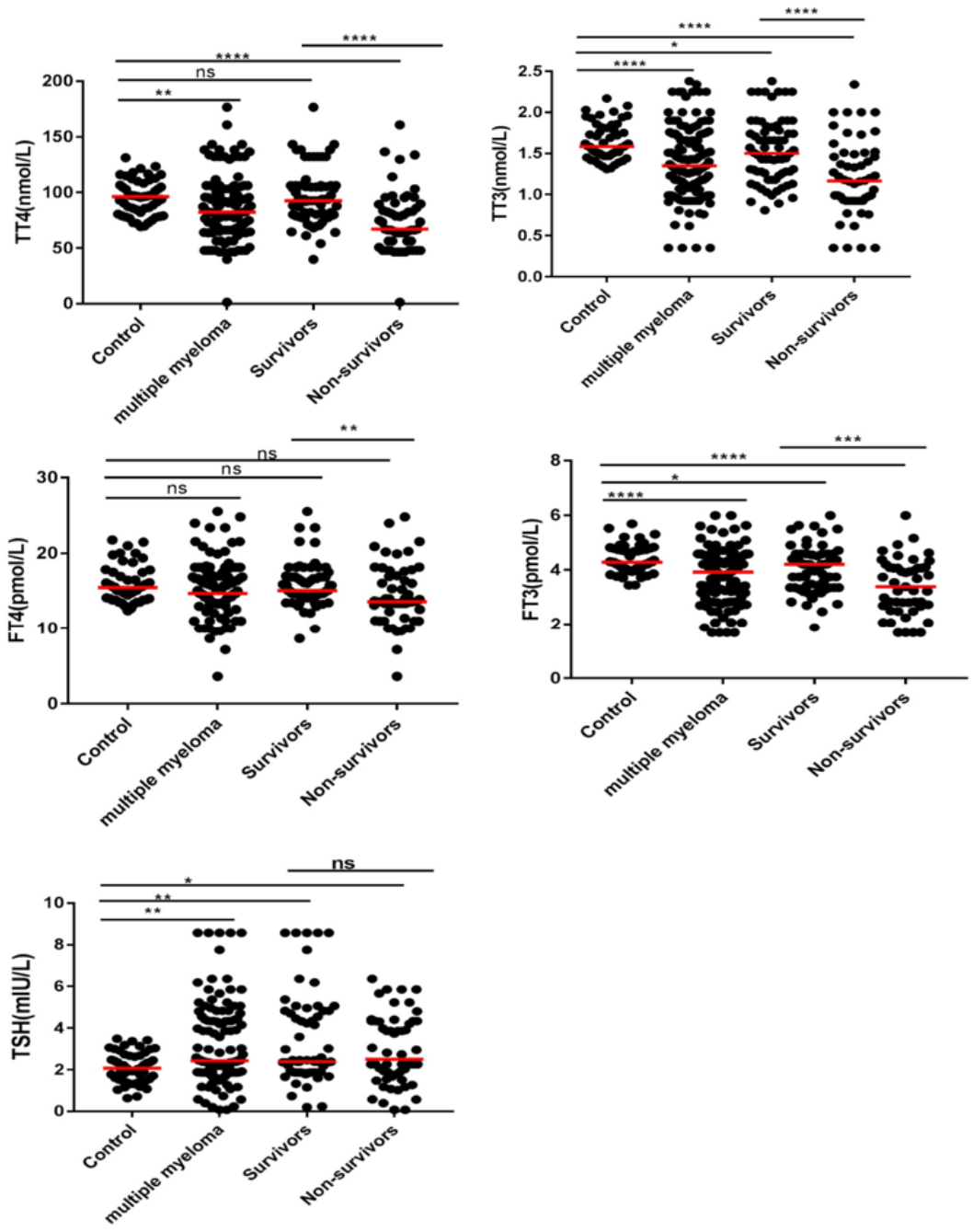

Figure 1

Comparison of thyroid function indexes among different groups.

The horizontal lines represent the median.Abbreviation: TSH ,Thyroid stimulating hormone;TT4,Total thyroxine; TT3,Total triiodothyronine; FT4 , Free thyroxine ;FT3 ,Free triiodothyronine.

* P < 0.05; ** P < 0.01; ***P < 0.001; **** P < 0.0001; ns, not significant.

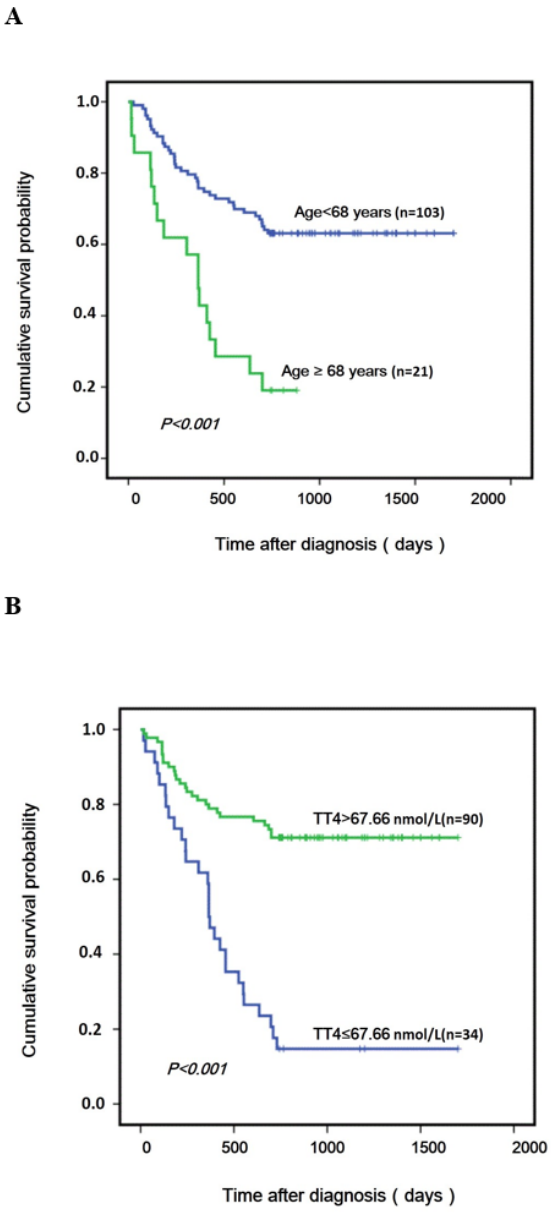

Figure 2

Kaplan–Meier curves for overall survival (OS) in MM patients with A age≥68years or age<68 years , B TT4≤67.66 nmol/L or TT4>67.66 nmol/L.

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