Correlation Between Serum Thyroid Hormone Levels and In-Hospital Prognosis in Patients with Heart Failure (Postprint)

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Abstract

Background: In clinical practice, the authors observed that serum reverse triiodothyronine (rT3) levels were often markedly elevated above the upper limit of the biological reference interval in heart failure patients who died during hospitalization. Previous studies investigating the predictive value of thyroid hormones for in-hospital mortality in heart failure patients, particularly regarding the predictive value of rT3, are scarce. Identifying indicators with predictive value for in-hospital death in heart failure patients holds significant clinical importance. Objective: To investigate the correlation between serum thyroid hormones and in-hospital prognosis in heart failure patients. Methods: A total of 197 heart failure patients hospitalized at Dongzhimen Hospital, Beijing University of Chinese Medicine from April 2019 to April 2022 were enrolled. Baseline data were collected through the electronic medical record system. All subjects underwent fasting venous blood sampling within 24 hours of admission to measure total triiodothyronine (TT3), total thyroxine (TT4), free triiodothyronine (FT3), free thyroxine (FT4), thyroid-stimulating hormone (TSH), rT3, and N-terminal pro-brain natriuretic peptide (NT-pro-BNP). Patients were divided into a death group (n=18) and a non-death group (n=179) based on in-hospital mortality. Multivariate Logistic regression analysis was employed to identify factors influencing in-hospital mortality. Receiver operating characteristic (ROC) curves were constructed to evaluate the predictive value of relevant indicators, the area under the curve (AUC) was calculated, and Delong's test was used to compare AUCs among indicators. Results: The death group exhibited higher age and rT3 levels, and lower FT3, TT3, and TSH levels compared with the non-death group ($P<0.05$). In the non-death group, 66 patients had normal thyroid function, 87 had low T3 syndrome, 15 had isolated high FT4, 3 had isolated high TT4, 5 had both high TT4 and FT4, 1 had isolated low TT4,

1 had isolated high TT3, and 1 had isolated high FT3. In the death group, 1 patient had normal thyroid function, 14 had low T3 syndrome, and 3 had isolated high FT4. The incidence of low T3 syndrome differed significantly between the two groups (P<0.05). Multivariate Logistic regression analysis identified rT3 as an independent factor influencing in-hospital mortality (P<0.05). ROC analysis revealed an AUC for rT3 of 0.914 [95%CI (0.865, 0.962)], which was superior to age (Z=3.137, P=0.002), FT3 (Z=2.389, P=0.017), TT3 (Z=2.123, P=0.034), and TSH (Z=3.056, P=0.002). Conclusion: Low T3 syndrome is a risk factor for in-hospital mortality in heart failure patients, and serum rT3 demonstrates high prognostic value for in-hospital outcomes, warranting increased clinical attention.

Full Text

Relationship between Serum Thyroid Hormone Levels and Prognosis during Hospitalization in Heart Failure Patients

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Abstract

Background: In clinical practice, we observed that serum reverse triiodothyronine (rT3) levels were markedly elevated above the upper limit of the biological reference interval in heart failure patients who died during hospitalization. Previous research on thyroid hormones as predictors of in-hospital mortality in heart failure, particularly regarding the predictive value of rT3, remains limited. Identifying predictive indicators for in-hospital death in heart failure patients carries significant clinical importance.

Objective: To investigate the correlation between serum thyroid hormones and in-hospital prognosis in heart failure patients.

Methods: We enrolled 197 heart failure patients hospitalized at Dongzhimen Hospital of Beijing University of Chinese Medicine between April 2019 and April 2022. Baseline data were collected through the electronic medical record system. Within 24 hours of admission, fasting venous blood samples were obtained from all participants to measure total triiodothyronine (TT3), total thyroxine (TT4), free triiodothyronine (FT3), free thyroxine (FT4), thyroid-stimulating hormone

(TSH), rT3, and N-terminal pro-brain natriuretic peptide (NT-pro-BNP). Patients were divided into a death group (n=18) and a non-death group (n=179) based on whether they died during hospitalization. Multivariate logistic regression analysis was used to identify factors influencing in-hospital mortality. Receiver operating characteristic (ROC) curves were constructed to evaluate the predictive value of relevant indicators, with areas under the curve (AUC) calculated and compared using the Delong test.

Results: The death group exhibited significantly higher age and rT3 levels, and lower FT3, TT3, and TSH levels compared to the non-death group (P<0.05). In the non-death group, 66 patients had normal thyroid function, 87 had low T3 syndrome, 15 had isolated high FT4, 3 had isolated high TT4, 5 had both high TT4 and FT4, 1 had isolated low TT4, 1 had isolated high TT3, and 1 had isolated high FT3. In the death group, 1 patient had normal thyroid function, 14 had low T3 syndrome, and 3 had isolated high FT4. The incidence of low T3 syndrome differed significantly between the two groups (P<0.05). Multivariate logistic regression analysis identified rT3 as an independent influencing factor for in-hospital mortality (P<0.05). ROC curve analysis revealed that rT3 had an AUC of 0.914 [95%CI (0.865, 0.962)], which was superior to age (Z=3.137, P=0.002), FT3 (Z=2.389, P=0.017), TT3 (Z=2.123, P=0.034), and TSH (Z=3.056, P=0.002).

Conclusion: Low T3 syndrome represents a risk factor for in-hospital death in heart failure patients. Serum rT3 demonstrates high predictive value for prognostic assessment during hospitalization and warrants greater clinical attention.

Keywords: heart failure; low T3 syndrome; reverse triiodothyronine; thyroid hormone; prognosis; influencing factor analysis

Introduction

Heart failure represents the terminal stage of cardiac disease caused by multiple etiologies, with persistently high mortality and rehospitalization rates [1-2]. In clinical practice, we have observed that low T3 syndrome accounts for a substantial proportion of hospitalized heart failure patients, and serum reverse triiodothyronine (rT3) values in those who die during hospitalization are often markedly elevated above the biological reference interval upper limit. Identifying predictive indicators for in-hospital mortality in heart failure patients holds significant clinical importance. Previous studies have suggested that triiodothyronine (T3) and rT3 levels may serve as markers for disease assessment and prognosis in heart failure [3-4]; however, research on thyroid hormones as predictors of in-hospital death, particularly regarding the predictive value and mechanisms of rT3, remains limited. This study aims to explore the relationship between serum thyroid hormones and in-hospital prognosis in heart failure patients, seeking to identify thyroid hormone indicators with predictive value for in-hospital mortality to assist clinical decision-making.

Methods

Study Population

We enrolled 197 heart failure patients hospitalized at Dongzhimen Hospital of Beijing University of Chinese Medicine between April 2019 and April 2022. Inclusion criteria comprised a diagnosis of heart failure according to the "Chinese Guidelines for the Diagnosis and Treatment of Heart Failure 2018" [1]. Exclusion criteria included: (1) acute myocardial infarction; (2) thyroid diseases such as hyperthyroidism or hypothyroidism; (3) severe primary conditions including respiratory failure or hepatic/renal insufficiency; (4) severe infection; (5) pregnancy or lactation; and (6) current use of thyroid-related medications or iodine-containing agents such as amiodarone or contrast media. This study was approved by the Medical Ethics Committee of Dongzhimen Hospital of Beijing University of Chinese Medicine (Ethics No. 2018-JYBZZ-JS093), and all patients provided informed consent.

Data Collection

Baseline data were collected through the electronic medical record system. Within 24 hours of admission, fasting venous blood samples were obtained from all participants to measure TT3, TT4, FT3, FT4, TSH, rT3, and NT-pro-BNP.

Definitions and Diagnostic Criteria

Reference ranges were as follows: TT3 1.02–2.48 nmol/L; TT4 70.01–152.51 nmol/L; FT3 3.30–6.48 pmol/L; FT4 7.59–16.09 pmol/L; TSH 0.49–4.91 mU/L; and rT3 0.20–0.95 g/L. Low T3 syndrome was diagnosed based on reduced FT3 or TT3 levels, elevated rT3, and normal or decreased TSH [5]. Cardiac function was classified according to the New York Heart Association (NYHA) functional classification as grades I–IV.

Grouping

Patients were divided into a death group (n=18) and a non-death group (n=179) based on in-hospital mortality.

Statistical Analysis

Normally distributed continuous variables were expressed as mean ± standard deviation and compared between groups using independent samples t-tests. Non-normally distributed continuous variables were presented as median (P25, P75) and compared using the Mann-Whitney U test. Categorical data were expressed as frequencies and compared using the chi-square test. Multivariate logistic regression analysis was performed to identify factors influencing in-hospital mortality. ROC curves were constructed to evaluate the predictive value of relevant indicators, with AUCs calculated and compared using the Delong test. Statistical significance was defined as $P<0.05$.

Results

Comparison of Baseline Characteristics

The death group exhibited significantly higher age and rT3 levels, and lower FT3, TT3, and TSH levels compared to the non-death group (P<0.05). No significant differences were observed in gender distribution, FT4, TT4, or NT-pro-BNP between the two groups (P>0.05) .

Thyroid Function Status

In the non-death group, 66 patients had normal thyroid function, 87 had low T3 syndrome, 15 had isolated high FT4, 3 had isolated high TT4, 5 had both high TT4 and FT4, 1 had isolated low TT4, 1 had isolated high TT3, and 1 had isolated high FT3. In the death group, 1 patient had normal thyroid function, 14 had low T3 syndrome, and 3 had isolated high FT4. The incidence of low T3 syndrome differed significantly between the two groups (^{2}=0.12, P<0.05).

Multivariate Logistic Regression Analysis

Using in-hospital mortality (non-death group=0, death group=1) as the dependent variable and variables showing significant differences in baseline comparisons (age, FT3, TT3, TSH, rT3) as independent variables, multivariate logistic regression analysis revealed that rT3 was an independent influencing factor for in-hospital mortality in heart failure patients (P<0.05) .

Predictive Value of Age, FT3, TT3, TSH, and rT3

ROC curve analysis demonstrated that rT3 had an AUC of 0.914 [95%CI (0.865, 0.962)] for predicting in-hospital mortality, which was superior to age (Z=3.137, P=0.002), FT3 (Z=2.389, P=0.017), TT3 (Z=2.123, P=0.034), and TSH (Z=3.056, P=0.002) [Figure 1: see original paper] .

Discussion

Heart failure results from abnormal cardiac structure and/or function due to various causes, leading to impaired ventricular systolic and/or diastolic function. As a severe manifestation or advanced stage of cardiac disease, it produces a complex clinical syndrome characterized by dyspnea, fatigue, limited exercise capacity, fluid retention (pulmonary and systemic congestion), and impaired venous return [1]. The China Hypertension Survey (CHS) 2012–2015, which analyzed 22,158 Chinese residents, reported a heart failure prevalence of 1.3% among individuals aged $ $35 years [6]. The 2020 China Heart Failure Medical Quality Control Report, analyzing 33,413 hospitalized heart failure patients with recorded outcomes from January 2017 to October 2020, documented an in-hospital mortality rate of 2.8% [7].

Thyroid hormones, synthesized and secreted by the thyroid gland, regulate metabolism and growth development, acting on most human cells. The cardiovascular system represents a crucial target organ for thyroid hormones. Previous studies have indicated that heart failure often manifests as low T3 syndrome, which is closely associated with clinical prognosis [8-10]. Low T3 syndrome is characterized by decreased serum T3, increased rT3, and normal or reduced TSH levels. In our study, the incidence of low T3 syndrome was significantly higher in the death group compared to the non-death group, suggesting that low T3 syndrome may be a risk factor for in-hospital mortality in heart failure patients.

While numerous studies have demonstrated the relationship between thyroid hormone levels and prognosis in heart failure patients [11-13], research on predictors of in-hospital mortality remains relatively scarce. Iglesias et al. [14] reported that decreased FT3 levels represent an independent predictor of in-hospital death in elderly heart failure patients. Our comprehensive analysis of gender, age, thyroid hormones, and NT-pro-BNP in relation to in-hospital mortality revealed that rT3 serves as both an influencing factor and a predictive indicator for in-hospital death in heart failure patients.

Reverse T3 is formed through the deiodination of T4 by type 3 iodothyronine deiodinase in peripheral tissues, representing a biologically inactive metabolite of T4 that maintains a specific ratio with serum T3 and T4 [15]. Clinically, rT3 measurement primarily aids in differentiating hypothyroidism from low T3 syndrome; the former shows decreased T3, T4, and rT3 with elevated TSH, whereas the latter exhibits decreased T3, increased rT3, and normal or reduced TSH [16].

Under physiological conditions, serum rT3 levels can be influenced by patient age, with healthy individuals over 80 years showing significantly higher rT3 values compared to middle-aged and younger populations [17-18]. This age-related increase may reflect a protective mechanism, as reduced caloric requirements in the elderly lead to increased production of non-calorigenic rT3 and decreased T3 synthesis, preventing excessive metabolic consumption. In our previous study using the same detection equipment, we established normal biological reference intervals for rT3 using an indirect method, finding that the mean rT3 level in individuals over 80 years was (0.79$±$0.10) g/L, higher than all younger age groups [18]. In the current study, the 18 heart failure patients who died had a median age of 84 years, with rT3 values at P25, median, and P75 of 1.33 g/L, 1.69 g/L, and 2.74 g/L, respectively—all substantially exceeding the average upper limit for their age group.

The markedly elevated rT3 levels in the death group and its superior predictive value over T3 for in-hospital mortality can be attributed to altered deiodinase activity in heart failure. Deiodination represents the primary mechanism for regulating thyroid hormone activity, catalyzed by three iodothyronine deiodinases (D1, D2, D3). T4 undergoes inner-ring deiodination to form rT3, while T3 undergoes inner-ring deiodination to form diiodothyronine (T2) under the action

of D1 and D3; conversely, T4 undergoes outer-ring deiodination to form T3, and rT3 undergoes outer-ring deiodination to form T2 through D1 and D2 activity. D1, predominantly expressed in the liver and kidneys, constitutes the primary pathway for rT3 clearance, whereas D3 is the main pathway for rT3 generation [19-20]. Heart failure patients who die during hospitalization often exhibit hepatic and renal insufficiency, impairing D1 activity in these organs and reducing rT3 clearance. Additionally, systemic congestion, chronic tissue hypoxia, and the hypoxic and inflammatory myocardial microenvironment in heart failure can alter deiodinase activity and deiodination pathways, such as increased D3 expression leading to enhanced conversion of T3 to inactive T2 and T4 to rT3, resulting in elevated serum rT3 [21-22]. Furthermore, thyroid hormones directly affect cardiomyocytes by increasing contractility and myocardial oxygen consumption while accelerating heart rate. In the death group, increased production of inactive rT3 led to reduced myocardial contractility, decreased stroke volume, increased left ventricular end-systolic volume, accelerated left ventricular remodeling, worsening heart failure, and further rT3 elevation, creating a vicious cycle.

Currently, most hospitals routinely measure only the five-item thyroid panel (TT3, TT4, FT3, FT4, TSH) in clinical practice, with rT3 not being a standard test item, which explains the relative scarcity of previous research on rT3 for predicting in-hospital mortality in heart failure. Our hospital's "complete thyroid function panel" includes 10 items comprising TT3, TT4, FT3, FT4, TSH, and rT3, providing data support for this study as most heart failure patients undergo this comprehensive testing to exclude thyroid disease upon admission.

This study has several limitations: it represents a single-center retrospective analysis with a relatively small sample size, and we did not include other potential prognostic indicators such as echocardiographic findings or additional hematological parameters. These aspects will be addressed in future research.

In summary, low T3 syndrome constitutes a risk factor for in-hospital death in heart failure patients, and serum rT3 demonstrates high predictive value for prognostic assessment during hospitalization. We recommend that rT3 testing be performed in hospitalized heart failure patients.

Author Contributions: ZHANG Jin conceived the primary research objectives, designed the study, supervised implementation, and drafted the manuscript. DING Zhiguo revised the manuscript. LI Ying, LI Weiqiang, and ZHANG Yuanyuan collected and organized data and performed statistical analysis. ZHOU Tong was responsible for quality control, overall article supervision, and project management.

Conflict of Interest: The authors declare no conflicts of interest.

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