Clinica Chimica Acta 494 (2019) 31–37

Contents lists available at ScienceDirect

Clinica Chimica Acta

journal homepage: www.elsevier.com/locate/cca

Predictive value of combined serum FGF21 and free T3 for survival in septic patients

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ARTICLE INFO

Keywords:
Fibroblast growth factor 21
Thyroid hormone
Sepsis
Mortality

ABSTRACT

Background: We examined the correlation between thyroid hormone (TH) concentrations and the serum fibroblast growth factor 21 (FGF21) concentration in septic patients and to assess the collaborative value of these factors in predicting 28-day mortality in septic patients.

Methods: A total of 120 consecutive patients with sepsis were divided into two groups according to their survival or death within 28 days after initial diagnosis of sepsis.

Results: Patients in the non-survivor group had significantly higher serum FGF21 concentrations but lower total and free triiodothyronine (T3) and tetraiodothyronine (T4) concentrations than those in the survivor group. Thyroid hormone concentrations, including T3, free T3, T4 and free T4, were significantly negatively correlated with the ΔSOFA and APACHE II scores as well as the serum FGF21, IL-6, tumor necrosis factor-α, IL-10, procalcitonin, and C-reactive protein concentrations. Logistic regression analysis showed that the ΔSOFA score, serum FGF21 concentration, and free T3 concentration were significant predictors of 28-day mortality. The model with variables of ΔSOFA score and serum FGF21 and free T3 concentrations had the greatest area under the curve of 0.969.

Conclusion: The addition of free T3 and serum FGF21 to ΔSOFA score provided a significantly improved ability to predict 28-day mortality in septic patients.

1. Introduction

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection [1]. Organ dysfunction can be quantitatively identified as an acute change in the total Sequential Organ Assessment (SOFA) score ≥ 2 points due to infection [1]. Current studies focus on the ability to inflammation biomarkers (such as procalcitonin [PCT] and C reactive protein [CRP] to predict progression of sepsis and have shown that these markers have limited capacity for prognostic determination. PCT has shown poor efficacy for predicting mortality in septic patients, and the ability of CRP to predicting septic patients' mortality is still in dispute [2–4]. Therefore, efforts to explore the value of other sepsis-related markers for predicting sepsis progression are necessary.

During sepsis, consistent with a systemic inflammatory reaction, a hypermetabolic state occurs in order to provide the energy needed to sustain the highly upregulated immune response upon pathogen invasion [5]. Thus, both metabolic adaptation and a pro-inflammatory response as well as a compensatory anti-inflammatory response are all important parts of the sepsis process [6]. These 3 pathophysiological facets could be concurrently taken into consideration in the search for a new model to better predict sepsis progression.

Thyroid hormone plays a pivotal role in the adaptation of metabolic function to stress and critical illness. The serum concentration of thyroid hormone can be affected during the course of sepsis, which is known as non-thyroidal illness syndrome [7]. It is marked by significantly decreased serum concentrations of free and total triiodothyronine (T3) and increased concentrations of reverse T3 (rT3). With differing severity of illness, low total or free tetraiodothyronine (T4) and sometimes low thyroid-stimulating hormone (TSH) can also be observed [8]. A low free T3 or free T4 concentration is considered to be closely associated with the severity of disease and mortality in the intensive care unit [9].

Fibroblast growth factor (FGF) 21, a member of the FGF family, is a

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https://doi.org/10.1016/j.cca.2019.03.005
Received 28 December 2018; Received in revised form 28 February 2019; Accepted 6 March 2019
Available online 07 March 2019
0009-8981/

polypeptide with 210 amino acids that is predominantly produced by the liver [10]. FGF21 possesses diverse metabolic activities, as it regulates lipid and glucose metabolism, stimulates ketogenesis, and improves insulin sensitivity [11,12]. Recently, FGF21 has been found to exert an anti-inflammatory effect by directly inhibiting macrophage-mediated inflammation [13]. FGF21 appears to have a role in modulating inflammation in an experimental pancreatitis model [14]. A possible role for FGF21 in sepsis has been demonstrated by the observation of increased circulating concentrations of FGF21 in mice in response to toxic effects of lipopolysaccharide (LPS) [15]. In addition, serum FGF21 concentrations are increased in patients with sepsis as compared with healthy controls, suggesting a role for FGF21 in the severe inflammation response [16]. Our previous works showed that septic patients who died within 28 days had a significantly higher FGF21 concentration compared with those who survived; moreover, serum FGF21 concentration was found to be an independent predictor of 28-day mortality in patients with sepsis [17]. These findings highlight the possible role of FGF21 as a prognostic marker in patients with sepsis.

Multiple studies have demonstrated a mutual-modulating relationship between FGF21 and thyroid hormone (TH) [18–20]. In euthyroid mice, T3 promotes hepatic FGF21 mRNA expression by binding to its receptor in a peroxisome proliferator-activated receptor (PPAR)-α-dependent manner [18]. Increased serum FGF21 concentrations were found to be positively associated with free T3 and free T4 concentrations in patients with hyperthyroidism [19]. Conversely, peripheral FGF21 administration to diet-induced obese mice contributed to a modest decline in serum concentrations of T3 and T4 [20], while, interestingly, one study proved that FGF21 and thyroid hormone act independently in terms of energy metabolism in critical metabolic states [21]. However, to date, there has been no study exploring whether TH is associated with FGF21 in early sepsis or assessing their collaborative value in predicting 28-day mortality in septic patients.

2. Materials and methods

2.1. Study design and participants

This study was a continuous investigation using the same panel of patients from a prospective study [17]. A total of 120 consecutive patients with sepsis were included from the Changsha of Traditional Chinese Medicine Hospital, China during January to August 2017. Sepsis was diagnosed according to the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) [1]. None of the patients had an autoimmune thyroid disease, and they were with thyroid peroxidase antibody (TPO-Ab) and thyroglobulin antibody (Tg-Ab) negative. The patients were divided into two groups, survivors and non-survivors, according to their survival or death within 28 days after the initial diagnosis of sepsis. The study was approved by the Ethics Committee of Changsha of Traditional Chinese Medicine Hospital. All participants or their guardians provided written informed consent.

2.2. Data collection

Demographic data for each participant were collected, including age, gender, and underlying diseases. The vital signs of each patient were measured and recorded. Routine blood tests were conducted in the hospital's central laboratory, and the results of the tests were recorded. The ΔSOFA score as well as the acute physiology and chronic health evaluation II (APACHE II) score were calculated.

2.3. Measurement of cytokine concentrations

Blood samples were collected from each participant within 24 h after diagnosis. Serum concentrations of cytokines, including FGF21, IL-6, IL-10, tumor necrosis factor (TNF)-α, PCT, and CRP, were assayed using enzyme-linked immunosorbent assays (ELISAs, R&D Systems) according to the manufacturer's instructions.

2.4. Measurement of thyroid hormone concentrations

Fasting venous blood samples were collected from each participant for the measurement of the serum thyroid hormone concentrations. Serum concentrations of total T3, free T3, total T4, free T4 and TSH were measured on an automatic immunoassay analyzer (ADVIA Centaur XP, Siemens Healthcare Diagnostics) using the chemiluminescence method, according to the assay kit manufacturer's instructions (R &D Systems). All blood samples were assayed within 24 h of collection from participants.

2.5. Statistical analysis

The SPSS for Windows ver 24.0 software package was used for the statistical data analysis. For continuous data, the Kolmogorov-Smirnov test was used for testing normality. Quantitative data are expressed as mean ± SD values when normally distributed, or as median and quartile values when not normally distributed. The inter-group differences were compared using Student's *t*-test or Mann-Whitney *U* test according to the tests for normality. Categorical data are expressed as absolute values and percentages and were compared using the χ^2 or Fisher's exact test. Correlations between thyroid hormone concentrations and clinical parameters or serum markers were analyzed using the Spearman's rank correlation test. Multivariate logistic regression analyses were performed to identify risk factors for the prediction of 28-day mortality, with results reported as the odds ratio (OR) and 95% confidence interval (CI). For each model, a receiver operating characteristic (ROC) curve was constructed, and the area under the curve (AUC) as well as the 95% CI (binomial exact method) were calculated. Differences between AUCs were tested by pairwise comparison of ROC curves. Survival curves were plotted using the Kaplan–Meier method and compared using the log-rank test. $P < .05$ was considered statistically significant.

3. Results

3.1. Patient characteristics

This study included 88 survivors and 32 non-survivors who had a mean survival time of 7.8 ± 0.9 days. Among the 120 study participants, 85 (70.8%) were male, and no difference in gender was observed between the survivor and non-survivor groups. Patients in the survivor group were younger and had smaller ΔSOFA and APACHE II scores compared with patients in the non-survivor group (all $P < .0001$). The clinical characteristics of the septic patients in the survivor and non-survivor groups are shown in Table 1.

The patients in the non-survivor group had a significantly higher median serum concentration of FGF21 [5979.0 (1041–6978.4) pg/ml] than those in the survivor group [951.4 (32.3–6223.9) pg/ml], ($P < .0001$). Similarly, the non-survivors had significantly higher concentrations of serum lactate (LAC), CRP, PCT, TNF-α, IL-6 and IL-10, as compared with the survivors (all $P < .0001$, Table 2).

In the non-survivor group, the median concentrations of serum T3 and free T3 were 0.45 (0.06–1.23) nmol/l and 1.8 (1.0–3.3) pmol/l, and these concentrations were significantly lower than those in the survivors [0.91 (0.00–2.20) nmol/l, $P < .0001$ and 3.0 (0.5–13.8) pmol/l, $P < .0001$, respectively]. Similarly, the median concentrations of serum T4 [52.8 (23.1–77.8) nmol/l] as well as free T4 [10.4 (0.78–16.20) pmol/l] were significantly lower in the non-survivors as compared with the survivors [68.4 (14.8–151.3) nmol/l, $P = .0020$ and 13.7 (6.8–22.3) pmol/l, $P < .0001$, respectively]. The serum TSH concentration did not differ between the two groups ($P = .1410$, Table 2).

Table 1
Demographic and clinical characteristics of septic patients in the survivor and non-survivor groups.

Characteristics	Non-survivor group (n = 32)	Survivor group (n = 88)	P value
Age, years	68 ± 14	60 ± 17	0.0140
Male, n (%)	21 (65.6)	64 (72.7)	NS
Underlying disease, n (%)			
Coronary heart disease	14 (43.75)	23 (26.1)	< 0.0001
Hypertension	11 (34.4)	23 (26.1)	< 0.0001
Type 2 diabetes	4 (12.5)	3 (3.409)	< 0.0001
Chronic renal failure	6 (18.8)	8 (9.1)	< 0.0001
Chronic obstructive pulmonary disease	6 (18.8)	12 (13.6)	< 0.0001
Mean arterial pressure, mmHg	71 ± 18	88 ± 15	< 0.0001
Respiration rate, bmp	25 ± 7	22 ± 5	0.0080
Heart rate, bmp	114 ± 30	98 ± 18	0.0080
Temperature, °C	37.7 ± 1.4	37.4 ± 0.8	NS
White blood count, 10^9/l	15.0 ± 7.0	15.0 ± 6.8	NS
Platelet count, 10^9/l	154 ± 114	182 ± 93	NS
Lymphocyte count, 10^9/l	0.66 ± 0.39	0.84 ± 0.67	NS
Monocyte count, 10^9/l	0.77 ± 0.45	0.85 ± 0.46	NS
GCS score	7 (3–15)	11 (7–15)	< 0.0001
APACHE II score	21 (10–36)	12 (3 − 21)	< 0.0001
ΔSOFA score	11 (4–21)	5 (2–18)	< 0.0001
Survival time, days	7.8 ± 0.9	28 ± 0	< 0.0001

Quantitative data are shown as mean ± SD or median (interquartile ranges); Categorical data are expressed as absolute values (percentages).
GCS, Glasgow coma score; APACHE II, acute physiology and chronic health evaluation II; ΔSOFA, Δ sequential Organ Failure Assessment.

Table 2
The concentrations of serum markers and thyroid hormone levels of septic patients in the survivor and non-survivor groups.

Characteristics	Non-survivor group (n = 32)	Survivor group (n = 88)	P value
Lactate, mmol/l	4.5 (0.9–18.0)	2.5 (0.7–5.6)	< 0.0001
CRP, mg/l	130.7 (18.6–498.0)	93.0 (6.4–200.0)	< 0.0001
PCT, ng/ml	15.4(1.0–200.0)	2.7 (0.5–200.0)	< 0.0001
TNF-α, pg/ml	60.1 (10.6–215.4)	12.2 (5.8–102.1)	< 0.0001
IL-6, pg/ml	367.7 (37.3–498.2)	82.9 (2.9–462.6)	< 0.0001
IL-10, pg/ml	605.2 (40.1–798.7)	77.6 (3.8–668.6)	< 0.0001
T3, nmol/l	0.45 (0.06–1.23)	0.91 (0.00–2.20)	< 0.0001
Free T3, pmol/l	1.8 (1.0–3.3)	3.0 (0.5–13.8)	< 0.0001
T4, nmol/l	52.8 (23.1–77.8)	68.4 (14.8–151.3)	< 0.0001
Free T4, pmol/l	10.4 (0.78–16.20)	13.7 (6.8–22.3)	< 0.0001
TSH, MIU/l	0.41 (0.12–1.26)	0.54 (0.05–5.31)	NS
FGF21, pg/ml	5979.0 (1041–6978.4)	951.4 (32.3–6223.9)	< 0.0001

Quantitative data are shown as median (interquartile ranges).
CRP, C-reactive protein; PTC, procalcitonin; TNF, tumor necrosis factor; IL, interleukin; T3, Triiodothyronine; T4, tetraiodothyronine; TSH, thyroid-stimulating hormone; FGF21, fibroblast growth factor 21.

3.2. Correlations of thyroid hormone concentrations with clinical parameters and blood markers

The associations of thyroid hormone concentrations with severity scores and laboratory variables were evaluated using the Spearman rank correlation test. As shown in Table 3, thyroid hormone concentrations, including T3, free T3, T4 and free T4, were significantly negatively correlated with the ΔSOFA score as well as APACHE II score. Also, these thyroid hormone concentrations were negatively correlated with serum biomarkers of inflammation, including IL-6, TNF-α, IL-10, PCT and CRT, but not with LAC. FGF21 was found to be negatively correlated with T3 ($r = -0.275$, $P = .002$), free T3 ($r = -0.302$, $P = .001$), T4 ($r = -0.320$, $P < .0001$) and free T4 ($r = -0.201$, $P = .027$).

3.3. Logistic regression analysis to identify predictors of 28-day mortality in sepsis patients

Logistic regression analysis was conducted to predict 28-day mortality of patients with sepsis, with use of the independent variables: the presence or absence of coronary heart disease (CHD), hypertension, type 2 diabetes mellitus (T2DM), chronic obstructive pulmonary disease (COPD), or chronic kidney disease (CKD); ΔSOFA score; and serum concentrations of IL-6, TNF-α, IL-10, PCT, CRP, FGF21, LAC, T3, free T3, T4, and free T4 (Model 1). Three variables, ΔSOFA score (OR 3.835, 95% CI 1.741–8.577; $P = .001$), serum FGF21 concentration (OR 5.648, 95% CI 2.226–14.332; $P < .0001$), and serum free T3 concentration (OR 0.273, 95% CI 0.111–0.669; $P = .005$), were found to be significantly correlated with 28-day mortality in sepsis patients (Table 4). Then we constructed another logistic model with fewer independent variables (namely the presence or absence of CHD, hypertension, T2DM, COPD or CKD, ΔSOFA score, and LAC) by removing variables of inflammation markers and thyroid hormones. ΔSOFA (OR 5.509, 95% CI 2.625–11.561; $P < .0001$) and LAC concentration (OR 2.204, 95% CI 1.221–3.977; $P = .009$) were found to be risk factors for 28-day mortality. In Model 3, we removed the variable LAC without changing any other parameters of Model 2. The results showed that ΔSOFA was still a predictor for 28-day mortality (OR 5.909, 95% CI 2.994–11.662; P < .0001).

3.4. ROC curves for the 28-day mortality models

The ROC curves were constructed to compare the abilities of different biomarkers to predict 28-day mortality. For individual biomarkers, FGF21 exhibited the highest predictive ability for 28-day mortality (AUC 0.896, 95% CI 0.827 to 0.944), followed by ΔSOFA score (AUC 0.887, 95% CI 0.816 to 0.938) and free T3 (AUC 0.820, 95% CI 0.739 to 0.884), whereas LAC showed a modest predictive performance with an AUC of 0.762 (95% CI 0.675 to 0.835), as shown in Fig. 1A.

Then we constructed multi-biomarker models by combining free T3 and serum FGF21 with the ΔSOFA score (Model 1) or combining serum LAC with the ΔSOFA score (Model 2), to compare with the variable of ΔSOFA score only (Model 3). Model 1 with variables of ΔSOFA score, serum FGF21, and free T3 achieved the greatest AUC of 0.969 (0.920–0.992) (Table 5 and Fig. 1B). The AUC for prediction of 28-day mortality was 0.919 (0.855–0.961) for Model 2 with variables of ΔSOFA score and LAC and was 0.887 (0.816–0.938) for Model 3 with the variable of ΔSOFA score only. The differences in the AUCs were 0.050 between Model 1 and Model 2 ($P = .0052$), 0.032 between Model 2 and Model 3 ($P = .0313$), and 0.082 between Model 1 and Model 3 ($P = .0002$). These data suggested that Model 1, in terms of predictive capacity, outperformed Model 3 for 28-day mortality prediction.

3.5. Survival of septic patients with different sepsis mortality prediction models

Survival curves were constructed using the Kaplan–Meier method. In Model 1, by stratification at the probability cut-off value of 0.126 when achieving the highest AUC of 0.969, patients with a value ≥0.126 had a significantly shorter survival time (12.1 ± 0.5 days) than those with the a value < 0.126 (27.7 ± 0.3 days, $P < .001$, Fig. 2A). In Model 2, patients with a value ≥0.281 had a mean survival time of 13.3 ± 1.6 days, which was significantly shorter than that of patients with a value < 0.281 (27.0 ± 0.5 days, P < .001, Fig. 2B). Similarly, patients in Model 3 had a shorter survival time of 17.3 ± 1.5 days if they had a value ≥0.190, as compared with those who had a value < 0.190 (26.7 ± 0.6 days, P < .001, Fig. 2C).

Given that the actual survival time was 7.8 ± 0.9 days for non-survivors and 28 days for survivors, Model 1 exhibited better agreement with the actual survival than did Model 2 or Model 3 in septic patients.

Table 3
Correlations of thyroid hormone levels with clinical parameters and blood markers.

	T3		Free T3		T4		Free T4	
	Correlation coefficient	P value	Correlation coefficient	P value	Correlation coefficient	P value	Correlation coefficient	P value
APACHEII score	−0.445	< 0.0001	−0.479	< 0.0001	−0.365	< 0.0001	−0.264	0.004
ΔSOFA score	−0.446	< 0.0001	−0.405	< 0.0001	−0.419	< 0.0001	−0.349	< 0.0001
IL-6	−0.198	0.030	−0.216	0.018	−0.305	0.001	−0.243	0.007
TNF-α	−0.461	< 0.0001	−0.407	< 0.0001	−0.344	< 0.0001	−0.308	0.001
IL-10	−0.208	0.022	−0.234	0.010	−0.317	< 0.0001	−0.207	0.024
PCT	−0.475	< 0.0001	−0.420	< 0.0001	−0.420	< 0.0001	−0.307	0.001
CRP	−0.185	0.043	−0.198	0.030	−0.198	0.030	−0.158	NS
LAC	−0.135	NS	−0.130	NS	−0.130	NS	−0.049	NS
FGF21	−0.275	0.002	−0.302	0.001	−0.320	< 0.0001	−0.201	0.027

T3, Triiodothyronine; T4, tetraiodothyronine; APACHE II, acute physiology and chronic health evaluation II; ΔSOFA, Δ sequential Organ Failure Assessment; IL, interleukin; TNF, tumor necrosis factor; PTC, procalcitonin; CRP, C-reactive protein; LAC, Lactate; FGF21, fibroblast growth factor 21.

Table 4
Logistic regression analysis for prediction of 28-day mortality in septic patients.

	β	OR	95% CI	P value
Model 1				
ΔSOFA score	1.344	3.835	1.741–8.577	0.001
FGF21	1.731	5.648	2.226–14.332	< 0.0001
Free T3	−1.300	0.273	0.111–0.669	0.005
Model 2				
ΔSOFA score	1.706	5.509	2.625–11.561	< 0.0001
LAC	0.790	2.204	1.221–3.977	0.009
Model 3				
ΔSOFA score	1.776	5.909	2.994–11.662	< 0.0001

Model 1: Independent variables in the analysis consisted of the presence or absence of coronary heart disease (CHD), hypertension, type 2 diabetes mellitus (T2DM), chronic obstructive pulmonary disease (COPD) or chronic kidney disease (CKD), ΔSOFA score, IL-6, TNF-a, IL-10, PCT, CRP, FGF21, LAC, T3, free T3, T4 and free T4.
Model 2: Independent variables included the presence or absence of CHD, hypertension, T2DM, COPD, and CKD as well as the ΔSOFA score and LAC.
Model 3: Independent variables included the presence or absence of CHD, hypertension, T2DM, COPD, and CKD as well as ΔSOFA score.

Table 5
Comparison of AUCs for different prediction models.

	AUC	SE	95% CI[a]
ROC curve			
Model 1	0.969	0.0162	0.920–0.992
Model 2	0.919	0.0242	0.855–0.961
Model 3	0.887	0.0309	0.816–0.938
Difference in AUC			
AUC1 – AUC2[*]	0.050	0.0180	0.015–0.086
AUC1 – AUC3[#]	0.082	0.0217	0.039–0.124
AUC2 – AUC3[†]	0.032	0.0147	0.003–0.060

Model 1 with variables of ΔSOFA score, serum FGF21 and serum free T3; Model 2 with variables of ΔSOFA score and LAC; Model 3 with variable of ΔSOFA score.
[a] Binomial exact method.
[*] P = .0052
[#] P = .0002
[†] P = .0313.

4. Discussion

In this study, we identified the negative correlation between thyroid hormone concentrations (total and free T3, T4) and serum FGF21 concentration in patients with sepsis. Importantly, a combination of FGF21 and free T3 added to the traditional ΔSOFA score provides considerable improvement for assessing the risk of 28-day mortality in septic patients, suggesting the meaningfulness of a multi-marker strategy for the prediction of sepsis-related mortality.

We found a negative correlation between thyroid hormone concentrations and serum FGF21 concentrations in the early phase of

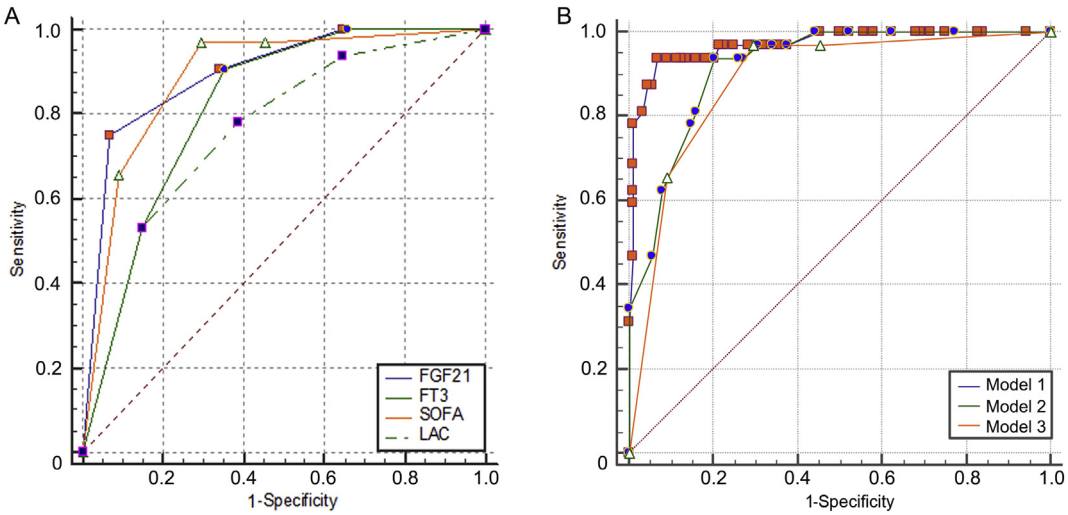

Fig. 1. ROC curves for the 28-day mortality models. A. The AUCs for individual biomarkers were 0.896 for FGF21, 0.887 for ΔSOFA score, 0.820 for free T3, and 0.762 for LAC. B. Model 1 with variables of ΔSOFA score, serum FGF21, and serum-free T3 achieved the greatest AUC of 0.969, as compared with Model 2 with variables of ΔSOFA score and LAC (AUC 0.919) and Model 3 with the variable of ΔSOFA score (AUC 0.887).

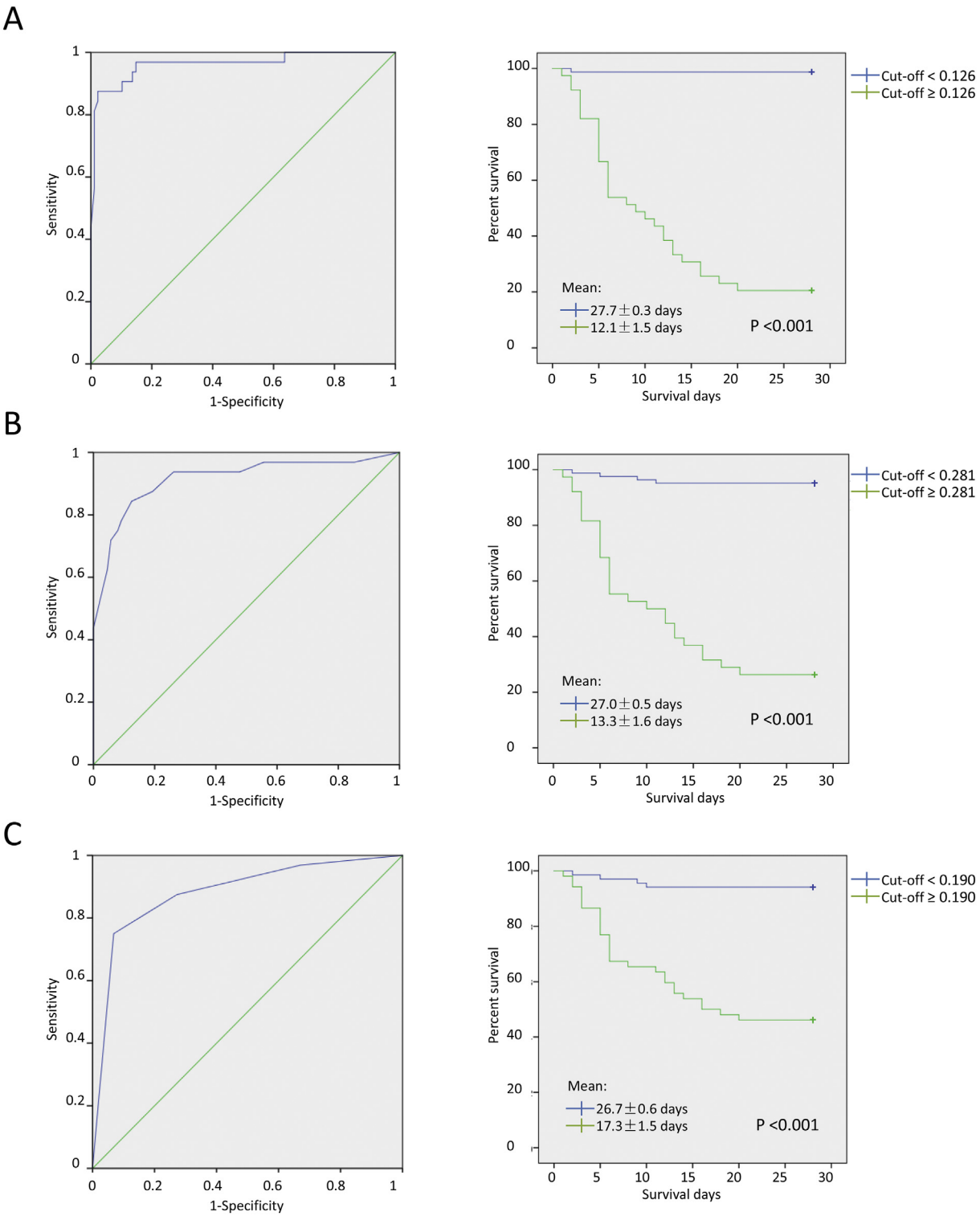

Fig. 2. Kaplan–Meier survival analysis in sepsis patients. ROC curves (left panel) and survival curves (right panel) were calculated for Model 1 (A, at the probability cut-off value of 0.126), Model 2 (B, at the cut-off value of 0.844), and Model 3 (C, at the cut-off value of 0.190).

sepsis. This can be partly explained by the metabolic aspect; the decrease in serum T3 during sepsis is an adaptive metabolic response to increase resistance to inflammation by lowering the cellular metabolic activity [22,23]. Sepsis is usually accompanied by hyperglycemia and lipid metabolism alterations [24,25]. During the early phases of sepsis, serum FGF21 increases to stimulate gluconeogenesis, fatty acid oxidation, and ketogenesis as positive energy metabolism [26]. This means that in the initial stage of sepsis, although the serum T3 concentration was kept low by inflammation cytokines [27], increased serum concentrations of FGF21 could still play a role in promoting metabolism to satisfy the demands of cells. Thus, they could present a negative association. The negative association between thyroid hormone and serum FGF21 can also be attributed to the inflammatory response. Our study showed that free T3 was negatively associated with IL-6 and TNF-α. This was consistent with a previous study concluding that IL-6 and TNF-α can suppress thyroid hormone concentrations to different degrees

[27]. In contrast, our data demonstrated that serum FGF21 concentrations increased concurrently with serum IL-6, TNF-α concentrations. This illustrates that FGF21 plays a pivotal role in anti-inflammation at the initial stage of sepsis [28]. These opposing changes in the early phase of sepsis may also explain their inverse correlation.

We found that total and free T3 or T4 concentrations were lower in non-survivors than in survivors. These hormones were negatively correlated with the severity of sepsis according to the APACHE II score and ΔSOFA score, and classic indicators such as IL-6, TNF-a, and CRP. These findings were consistent with the results of a previous study, which demonstrated that serum T3 was negatively and strongly correlated with IL-6 ($r = -0.49$) and CRP ($r = -0.33$) [29]. Furthermore, our study showed that the basal serum T3 concentration was a strong predictive factor for assessing the risk of 28-day mortality. Consistent with this result, a systematic review also illustrated that thyroid dysfunction at baseline is associated with a worse prognosis of patients with sepsis or septic shock [30].

The combination of multiple biomarkers may provide a more comprehensive and valuable means for improving the risk of stratification of critically ill patients [31]. Previous studies performed in critically ill patients have demonstrated that tests that consider the baseline thyroid function can be added to the predictive capacity of the APACHE score [32,33]. Sepsis is a complex and multifactorial disorder, and its progression encompasses a multitude of scenarios by balancing microbial invasion and the compensatory host response. Given the complexity of this multi-system disorder, a single biomarker may be insufficient to assess the prognosis of septic patients with acceptable accuracy. Therefore, in the current study assessing the prognosis of septic patients, we combined different biomarkers of various pathophysiological aspects of sepsis, e.g., thyroid hormones, anti-inflammatory cytokines, and multi-organ dysfunction score. Our data showed that the ΔSOFA score alone could predict patients' outcomes, which was consistent with a previous study [34]. In addition, testing baseline serum LAC concentrations enhanced the whole model's accuracy for predicting sepsis mortality. Of importance, when integrating the anti-inflammatory biomarkers serum FGF21 and free T3 concentration into a model together (model 1), the AUC increased to the maximum of 0.969 for mortality prediction in this study population. The AUC for Model 1 was 8% greater than that for Model 3. This indicated that Model 1 had a better efficacy for predicting 28-day mortality in this group of patients, and these results are supported by the subsequent survival analysis. This new model contains metabolism and anti-inflammation characteristics of sepsis, allowing for better precision in predicting septic patients' mortality from additional stereoscopic information. The enhanced prediction precision of Model 1 might be beneficial for screening septic patients who need much more vigorous treatment. Further multi-center studies are needed to verify our findings.

This study has limitations. First, this was a clinical observational study, and thus, further mechanistic studies are required to elucidate the underlying mechanisms for why TH and FGF21 are negatively with each other in sepsis. Second, we did not measure the metabolism of septic patients directly due to a paucity of related equipment, and thus, we did not analyze the direct relationships among TH, FGF21, and metabolic state. Third, the changes in both TH and serum FGF21 are dynamic over time in response to treatment. Their change might be also useful in predicting patients' progression. Further research could evaluate the relationships between their dynamic changes and septic patients' mortality.

In conclusion, the serum concentration of thyroid hormone (free and total T3 and T4) was inversely correlated with the serum FGF21 concentration in patients with sepsis in the early stage. The addition of free T3 and serum FGF21 to the ΔSOFA score significantly improved the ability to predict 28-day mortality in septic patients.

Acknowledgements

This work was supported by Scientific Research of Health and Family Planning Commission of Hunan Province in 2015.

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