Nonthyroidal illness syndrome in acute pancreatitis patients: an 8-year cohort study

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Abstract

Background: Nonthyroidal illness syndrome (NTIS) is common in critical illness and is associated with poor prognosis. The aim of this study was to find the prevalence, characteristics, and prognosis of NTIS and its correlation with outcomes in AP patients.

Methods: A retrospective review of AP patients with a diagnosis of NTIS from Jan 2012 to September 2020 was performed. The serum thyroidal hormone (TH) disturbances, as well as the demographic characteristics and clinical outcomes of the study patients, were collected and analyzed.

Results: Over the eight years, 183 included AP patients were diagnosed as NTIS, constituting an incidence of 64.7%. Patients with NTIS were admitted with worse condition based on the higher APACHE II score, SOFA score, Balthazar’s CT score, CRP and lower albumin than euthyroid patients. Also, these patients had a longer ICU duration (3, 2–10 vs 2, 0–3, days, \( P = 0.039 \)) and tended to be more likely to develop infected pancreatic necrosis (IPN) (15.3% vs 6.3%, \( P = 0.087 \)) and gastrointestinal fistula (6% vs 0%, \( P = 0.082 \)) than euthyroid patients. Free triiodothyronine (FT3) was found the best performance in predicting death compared by other well-recognized biomarkers.

Conclusion: NTIS is common in AP patients within 7 days after the onset of the disease. NTIS is associated with the worse characteristics at admission and poor outcome during the course. FT3 should be investigate as a potential biomarker in the prediction of death in AP patients.

Keywords: Nonthyroidal illness syndrome, Pancreatitis, Thyroid hormone
scores were manually calculated for each single patient. The present study was performed to evaluate the thyroid function and the prevalence, underlying mechanisms, and its correlation with clinical variables and prognosis of NTIS in adult patients with AP.

Method
Study design and participants
This study retrospectively screened all AP cases admitted to the Center of Severe Acute Pancreatitis, Department of General Surgery, Jinling Hospital, within 7 days from the onset of the disease, from Jan 2012 to September 2020. The diagnosis and classification of the severity of AP were according to the 2012 revision of the Atlanta Classification [15], based on at least two of the following three criteria: (i) abdominal pain suggesting AP, (ii) elevated serum amylase and/or lipase > 3 times the upper limit of normal, and (iii) characteristic AP computed tomography (CT) findings.

The exclusion criteria were as follows: (1) age less than 18 years or older than 70 years; (2) history of thyroidal, hypophyseal, or hypothalamic disease; (3) in pregnancy, with malignancy or autoimmune diseases, etc.; (4) medication history of thyroidal hormone or antithyroid drugs.

Data collection
All the data were extracted from an electronic database (APDatabase) which were collected prospectively. This study was approved by the institutional review board (No: 2020 JLPDMC-006). Routine written informed consent was obtained for data collection, storage, and academic use of data from all patients or next of kin at admission. Additional informed consent from individuals was waived due to the retrospective and anonymous nature of the current study.

The demographic data, diagnosis, imaging data, and management as well as clinical outcomes of the study subjects were collected. Levels of serum thyroidal hormone, including free triiodothyronine (FT3), total triiodothyronine (TT3), free thyroxin (FT4), total thyroxin (TT4), and thyroid-stimulating hormone (TSH) were investigated using the chemiluminescent microparticle immunoassay within the 24 h after admission. Other laboratory test results, including hemoglobin, hematocrit, platelet, C-reactive protein (CRP), IL-6, creatinine, and alanine aminotransferase (ALT) were obtained from the Central Laboratory of Jinling Hospital. Meanwhile, acute physiology and chronic health evaluation II (APACHE II) score and sequential organ failure assessment (SOFA) scores were manually calculated for each single patient.

Diagnostic criteria of NTIS
Nonthyroidal illness syndrome was defined as a low serum FT3 level (<3.1 pmol/L) without an elevated TSH level (<0.3 mIU/L). The normal ranges of serum thyroidal hormone and thyroid-stimulating hormone in our hospital were as follows: FT3, 3.1–6.5 pmol/L; TT3, 1.23–3.07 nmol/L; FT4, 7.9–17.2 pmol/L; TT4, 71–161 nmol/L; and TSH, 0.3–4.5 mIU/L. According to symptoms and thyroid function assays tested within 24 h after admission, patients were categorized into five groups: euthyroid, NTIS, subclinical hypothyroidism, subclinical hyperthyroidism, and hypothyroidism.

Statistical analysis
Data involving demographics, AP etiologies, underlying diseases, smoking and drinking, clinical outcomes and management were compared between patients in the euthyroid and the NITS groups. The categorical variables (sex, etiology, underlying disease, smoking, drinking, clinical outcome, et al.) were described using frequency and percentage. Continuous variables (age, BMI, severity score, laboratory tests, TH and TSH levels, et al.) were described using mean values ± SD or median with interquartile range (IQR). We used the t-test to compare the continuous variables of the normal distribution, and the Mann–Whitney U tests compare the nonnormally distributed variables. For categorical variables, a chi-square test or Fisher exact test was used. Statistical significance was set at two-sided P < 0.05. Area Under the Curve of the Receiving Operating Characteristic Curve (AUCROC) analysis was used to define the optimal cutoff point of some important factors to predict the death in AP patients.

All data were analyzed using SPSS 19.0 statistical software (SPSS Inc., Chicago, IL).

Results
In our study, a total of 283 patients were included eventually. As shown in Fig. 1, the included patients were divided into five groups according to the thyroidal characteristics of each group listed at the bottom. Among them, 48 (48/283, 17.0%) patients were euthyroid with normal FT3, FT4 and TSH levels. One hundred and eighty-three patients (183/283, 64.7%) were diagnosed as NITS with a low serum FT3 level without elevated TSH level. NITS patients were subdivided into two groups: low FT3 only group (97/183, 43.0%) and low FT3 with concomitant low TSH group (86/183, 47.0%). Five patients (5/283, 1.8%) were classified as subclinical hypothyroidism, 41 patients (41/283, 14.5%) as subclinical hyperthyroidism and 5 patients (5/283, 1.8%) as...
subclinical hyperthyroidism based on the serum FT3 and TSH level.

**Baseline characteristics**

demographics and baseline characteristics of patients between the euthyroid group and the NITS group are listed in Table 1. Patients in the NTIS group were admitted with higher APACHE II score (6.9 ± 5.0 vs 4.1 ± 3.5, \( P < 0.001 \)), SOFA score (2.5 ± 3.0 vs 1.2 ± 1.9, \( P < 0.001 \)), CTSI score (6.3 ± 2.0 vs 4.9 ± 1.7, \( P < 0.001 \)), CRP (154.1 ± 79.9 vs 127.0 ± 81.3, mg/L, \( P = 0.039 \)) and lower albumin (30.9 ± 4.3 vs 33.0 ± 5.8, g/L, \( P = 0.004 \)) with a significant difference. And the Patients in the NITS had less percentage of hypertension (33/183, 18.0% vs 16/48, 33.3%, \( P = 0.021 \)). However, there was no difference in demographics (age, sex and BMI) and the distribution of AP etiology and diabetes mellitus (DM).

The level of serum thyroid hormone and thyroid-stimulating hormone are presented in the Table 2. The FT3 (2.5, 2.2–2.8, vs 3.4, 3.3–4.3, \( P < 0.001 \)), FT4 (9.0, 7.8–10.5 vs 10.6, 9.3–11.5, \( P < 0.001 \)), TT3 (0.4, 0.3–0.5 vs 0.6, 0.3–0.6, \( P < 0.001 \)), TT4 (59.0, 45.7–74.5 vs 75.3, 62.3–90.6, \( P < 0.001 \)) and TSH (0.5, 0.3–0.9 vs 0.9, 0.6–1.7, \( P < 0.001 \)) were significantly lower in the NITS group than in the euthyroid group. The level of thyroglobulin (TG) (4.4, 2.5–8.2 vs 6.1, 3.2–8.7, \( P = 0.404 \)) and parathyroid

### Table 1 Baseline characteristics and clinical variables between Euthyroid and NTIS groups

| Variables                      | All \( N = 231 \) | Euthyroid Group \( N = 48 \) | NITS Group \( N = 183 \) | \( P \) value |
|-------------------------------|------------------|-------------------------------|--------------------------|-------------|
| Age, year, median (IQR)       | 47 (38.0–55.0)   | 48.5 (37.5–54.0)              | 47.0 (38.0–55.0)         | 0.666       |
| Sex, M/F                      | 173/92           | 36/12                         | 114/69                   | 0.101       |
| BMI, kg/m², median (IQR)      | 26.5 (24.1–28.3) | 26.2 (24.3–28.1)              | 26.7 (23.3–28.6)         | 0.432       |
| Etiology, n (%)               |                  |                               |                          |             |
| Biliary                       | 96 (41.6)        | 16 (33.3)                     | 80 (43.7)                | 0.194       |
| Alcohol                       | 10 (4.3)         | 2 (4.2)                       | 8 (4.4)                  | 0.950       |
| Hyperlipidema                 | 119 (51.5)       | 28 (58.3)                     | 91 (49.7)                | 0.288       |
| Others                        | 8 (3.5)          | 2 (4.2)                       | 6 (3.3)                  | 0.126       |
| Underlying diseases, n (%)    |                  |                               |                          |             |
| Hypertension                  | 49 (21.2)        | 16 (33.3)                     | 33 (18.0)                | 0.021       |
| DM                            | 44 (19.0)        | 9 (18.8)                      | 35 (19.1)                | 0.953       |
| Smoking, n (%)                | 14 (29.2)        | 4 (24.6)                      | 10 (24.6)                | 0.518       |
| Drinking, n (%)               | 13 (27.1)        | 42 (23.0)                     | 42 (23.0)                | 0.550       |
| APACHE II score, median (IQR) | 6.4 ± 4.9        | 4.1 ± 3.5                     | 6.9 ± 5.0                | \(< 0.001\) |
| SOFA score at admission, median (IQR) | 2.2 ± 2.9 | 1.2 ± 1.9                    | 2.5 ± 3.0                | \(< 0.001\) |
| Balthazar’s CT score, median (IQR) | 6.0 ± 2.0 | 4.9 ± 1.7                    | 6.3 ± 2.0                | \(< 0.001\) |
| CRP, mg/L, mean ± SD          | 148.5 ± 80.6     | 127.0 ± 81.3                  | 154.1 ± 79.9             | 0.039       |
| WBC, mean ± SD                | 11.5 ± 4.7       | 10.8 ± 4.6                    | 11.7 ± 4.8               | 0.260       |
| Hemoglobin, mean ± SD         | 110.5 ± 22.4     | 114.6 ± 22.6                  | 109.4 ± 22.3             | 0.155       |
| Albumin, g/L, mean ± SD       | 31.3 ± 4.7       | 33.0 ± 5.8                    | 30.9 ± 4.3               | 0.004       |

BMI: body mass index; IQR: interquartile range; DM: diabetes mellitus; APACHE II: acute physiology and chronic health evaluation II; SOFA: sequential organ failure assessment; CRP: C-reactive protein; WBC: white blood cell
hormone (PTH) (4.6, 2.6–9.1 vs 3.6, 2.3–7.2, \( P = 0.855 \)) showed no significant differences.

**Clinical outcomes**

The clinical outcomes of included patients are shown in Table 3. Acute pancreatitis patients (≤7 days from the onset of abdominal pain) with NITS diagnosed within the 24 h after admission had a longer ICU duration than the euthyroid group (3, 2–10 vs 2, 0–3, \( P = 0.039 \)) significantly and tended to have higher mortality but not significantly (18, 9.8% vs 1, 2.1%, \( P = 0.082 \)). Figure 2 compares the cumulative survival rates in the euthyroid and NTIS groups. Also, more percentage of AP patients with NITS developed infected pancreatic necrosis (IPN) (29, 15.3% vs 3, 6.3%, \( P = 0.087 \)) and gastrointestinal fistula (11, 6% vs 0, 0%, \( P = 0.082 \)) without significant difference compared with euthyroid patients. Along, the need for percutaneous catheter drainage (PCD) for pancreatic necrosis, which is the first step of a step-up method for pancreatic necrosis infection, was significantly more in the NITS group than the euthyroid group. What’s more, the requirement of open pancreatic necrosectomy tended to be higher in the NITS group. However, the percentage of other complications had no significant difference, including intra-abdominal hemorrhage, new onset of organ failure and multiple organ dysfunction syndromes (MODS).

**Evaluation of the prognostic value of the candidate predictors of death in AP patients**

The AUCROC for FT3 was 0.714 (95% CI 0.602–0.827) in predicting death in AP patients (Fig. 3). ROC analysis revealed that the serum FT3 cutoff point of 2.2 pmol/L

### Table 2 Thyroid hormones parameters between Euthyroid and NTIS groups

| Variables | All | Euthyroid Group | NITS Group | \( P \) value |
|-----------|-----|-----------------|------------|--------------|
| FT3 (pmol/L) | 2.6 (2.3–3.0) | 3.4 (3.3–4.3) | 2.5 (2.2–2.8) | < 0.001 |
| FT4 (pmol/L) | 9.4 (8.2–10.9) | 10.6 (9.3–11.5) | 9.0 (7.8–10.5) | < 0.001 |
| TT3 (nmol/L) | 0.4 (0.3–0.6) | 0.6 (0.4–0.8) | 0.4 (0.3–0.5) | < 0.001 |
| TT4 (nmol/L) | 62.5 (48.1–80.4) | 75.3 (62.3–90.6) | 59.0 (45.7–74.5) | < 0.001 |
| TSH (mU/L) | 0.6 (0.4–1.1) | 0.9 (0.6–1.7) | 0.5 (0.3–0.9) | < 0.001 |
| TG (μg/L) | 4.8 (2.8–8.2) | 6.1 (3.2–8.7) | 4.4 (2.5–8.2) | 0.404 |
| PTH (pmol/L) | 4.4 (2.5–7.9) | 3.6 (2.3–7.2) | 4.6 (2.6–9.1) | 0.855 |

FT3 free triiodothyronine; TT3 total triiodothyronine; FT4 free thyroxin; TT4 total thyroxin; TSH thyroid-stimulating hormone; TG thyroglobulin; PTH parathyroid hormone.

### Table 3 Clinical outcomes between Euthyroid and NTIS groups

| Outcomes | All N = 231 | Euthyroid Group N = 48 | NITS Group N = 183 | \( P \) value |
|----------|-------------|------------------------|--------------------|--------------|
| Hospital mortality, n (%) | 19 (8.2) | 1 (2.1) | 18 (9.8) | 0.082 |
| ICU duration, median (IQR), d | 3 (2–8) | 2 (0–3) | 3 (2–10) | 0.039 |
| Intra-abdominal hemorrhage, n (%) | 14 (6.1) | 1 (2.1) | 13 (7.1) | 0.194 |
| Gastrointestinal fistula, n (%) | 11 (4.8) | 0 (0) | 11 (6.0) | 0.082 |
| New onset OF, n (%) | | | | |
| Respiratory | 34 (14.7) | 7 (14.6) | 27 (14.8) | 0.976 |
| Renal | 17 (7.4) | 5 (10.4) | 12 (6.6) | 0.362 |
| Cardiovascular | 7 (3.0) | 1 (2.1) | 6 (3.3) | 0.667 |
| MODS | 35 (15.2) | 5 (10.4) | 30 (16.0) | 0.304 |
| IPN, n (%) | 31 (13.4) | 3 (6.3) | 29 (15.3) | 0.087 |
| PCD, n (%) | 34 (14.7) | 2 (4.2) | 32 (17.5) | 0.020 |
| Open pancreatic necrosectomy, n (%) | 10 (4.3) | 0 (0) | 10 (5.5) | 0.098 |

IQR interquartile range; ICU intensive care unit; OF organ failure; MODS multiple organ dysfunction syndromes; IPN infected pancreatic necrosis; PCD percutaneous catheter drainage.
had optimal predictive value for the death in AP patients. We compared the FT3 with other common serum laboratory tests, including WBC, CRP and Alb in predicting the death of AP patients by ROC analysis, showing that FT3 was of the best performance.

Discussion

To our knowledge, the present 8-year population-based retrospective study is the largest clinical investigation of the TH disturbances (< 7 days after the onset of disease) and the first study to explore the role of NTIS in AP patients. Furthermore, we identified FT3 as a valuable predictor of the death of AP patients among the TH, which showed the best predictive performance compared with routine biomarkers by the ROC analysis.

NITIS are present in more than half of included AP patients with a prevalence of 64.7%. There is some possible pathogenesis: (1) in the acute phase of AP, patients are in a poor nutritional status treated with fasting, which induces a decrease in serum TH through a multifactorial mechanism including a decrease in serum leptin, and downregulation of hypothalamus-hypophysis-thyroid axis, resulting in persistently low serum TSH level [16]. (2) activity of hepatic thyroxine 5′-deiodinase (deiodinases type 1, D1) is impaired in AP patients by hepatic injury through endotoxins, cytokines released by the inflammatory pancreas, etc., sequentially affecting the conversion from T4 to T3 [17–19]. (3) the reduced levels of thyroid hormone-binding protein and its impaired binding activity, thereby increase the clearance of the free hormone [20].

NTIS is commonly considered as an adaptive mechanism to the overall downregulate of metabolism in the organism to save energy in critically ill patients [21]. On the one hand, the important FT3 target organs, such as the liver and muscles, are affected by the decrease thyroid hormone, of which the downregulation metabolism might be beneficial in these patients. On the other hand, the critically ill patients with NTIS may develop some complications due to the low active organ, including intestine, cardiovascular, kidney, etc. [3, 22, 23].

For the clinical characteristics at admission, we discovered higher APACHE II, SOFA and CTSI scores, a higher serum CRP level and a lower serum albumin level in the NTIS group, which is consistent with the clinical characteristics of these patients reported previously [9, 22]. They were probably exposed to worse clinical outcomes and prognosis.

For the clinical outcome in these patients, the percent of developing IPN, along with the need for invasive intervention, including PCD and open pancreatic necrosectomy is higher in the NTIS group. IPN causes high overall mortality of around 5 percent in acute pancreatitis [24–26] As reported previously, serum FT3 can directly modulate immune responses, including increasing phagocytic activity of immune cells, lymphocyte proliferation, antibody production, cytokine production, cytokine receptor expression, and oxygen-free radical generation through both genomic and nongenomic mechanisms [27]. Further, iodothyronines may have the effect of local antimicrobial by releasing liberated iodide ions at the site of pancreatic necrosis [2]. What’ more, the longer ICU duration is found in the NTIS group than the euthyroid group, which reflected the slower recovery in NTIS due to the downregulated metabolism. So, Monitoring the TH level can help identify the population of the high risk of developing IPN in AP patients and predict the course of the disease.

Previous studies reported that FT3 was a valuable and feasible biomarker to evaluate and predict the classification of the AP severity [13, 14]. We found that FT3 is of the better predictive performance compared with other well-recognized clinical variables, including WBC, CRP and Alb by ROC analysis. WBC and CRP are inflammatory markers that are reported to determine the severity of AP [28]. Alb is exclusively synthesized in the liver and low serum Alb (< 35 g/L) was found independently associated with an increased risk of developing of persistent organ failure and death in acute pancreatitis [29–31]. FT3 is a biomarker reflecting thyroid function that respond early in the AP course or serve as a self-regulating mechanism to changes in

Fig. 3 The ROC analysis of FT3, CRP, WBC and Alb in the prediction of death in AP patients. ROC receiving operating characteristics, FT3 free triiodothyronine, CRP C-reactive protein, WBC white blood cell, Alb albumin
energy consumption [13]. FT3 may be useful, combined with other biomarkers, for the development of a therapeutic strategy and the ultimate improvement of the outcome.

There are certain limitations of the present study. Firstly, the low mortality in this study cohort makes the results of the ROC curves prone to bias. Moreover, this is a single-center retrospective study with limited sample size so that the association between NTIS and clinical outcomes does not necessarily imply causality. For the treatment, whether interventions aimed at regulating TH concentrations in patients with AP are beneficial has not been satisfactorily answered yet. More studies should be taken to investigate the effect of normalizing TH concentration in AP patients.

Conclusion
In conclusion, NTIS is common in adult patients with AP within 7 days after the onset of the disease. NTIS is associated with the worse characteristics at admission and poor prognosis during the course. FT3 is a potential biomarker in the prediction of death in AP patients.

Abbreviations
NTIS: Nonthyroidal illness syndrome; T3: Triiodothyronine; TSH: Thyroid-stimulating hormone; TH: Thyroid hormone; AP: Acute pancreatitis; MSAP: Moderately severe acute pancreatitis; SAP: Severe acute pancreatitis; MAP: Moderately acute pancreatitis; FT3: Free triiodothyronine; CT: Computed tomography; TT3: Total triiodothyronine; FT4: Free thyroxin; TT4: Total thyroxin; CRP: C-reactive protein; ALT: Alanine aminotransferase; APACHE II score: Acute physiology and chronic health evaluation II score; SOFA score: Sequential organ failure assessment score; BMI: Body mass index; SD: Standard deviation; AUCROC: Area under the curve of the receiving operating characteristic curve; DM: Diabetes mellitus; TG: Thyroglobulin; PTH: Parathyroid hormone; IPN: Infected pancreatic necrosis; PCD: Percutaneous catheter drainage; MODS: Multiple organ dysfunction syndromes; WBC: White blood cell.

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Authors’ contributions
CQ, ZHD and XJX: study design, CQ and ZHD: acquisition of data and statistical analysis, XJX, MM, KG and XQY: analysis and interpretation of data; CQ: drafting of the manuscript, ZHT and JK: critical revision of the manuscript, ZHT, JK and WQL: study supervision and guidance. All authors have read and approved the final version of this manuscript, including the authorship.

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Availability of data and materials
The datasets analysed during the current study are available from the corresponding author on reasonable request.

Declarations
Ethics approval and consent to participate
This study was approved by the institutional review board (No: 2020 JLAP-DMC-006). Routine written informed consent was obtained for data collection, storage; and academic use of data from all patients or next of kin at admission.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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