Research Square

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Association of Serum Total Triiodothyronine with Illness Severity in Emergency Department Patients with Acute Heart Failure Requiring ICU Admission: A Prospective Observational Study

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Abstract

Background and Objective:

Acute heart failure (AHF) remains a major contributor to cardiovascular morbidity and mortality, particularly in settings where access to advanced biomarkers may be constrained. During critical illness, patients frequently develop non-thyroidal illness syndrome (NTIS), characterised by reduced circulating T3 without primary thyroid dysfunction. This study aimed to evaluate the association between serum total triiodothyronine (T3) and established markers of illness severity in Emergency Department patients with AHF requiring ICU admission in a secondary-care setting in South India.

Methods:

A prospective observational study was conducted over 18 months at a single secondary-care hospital in South India. Adult patients presenting to the Emergency Department with AHF who were subsequently admitted to the ICU were consecutively enrolled. Serum total T3, T4, TSH, and NT-proBNP were assessed within 6 hours of presentation; APACHE II scores were calculated using the standard methodology based on the worst physiological values recorded during the first 24 hours of ICU care. Patients were stratified by T3 level (LT3S: <0.8 ng/mL vs. normal T3: ≥0.8 ng/mL). Group comparisons used the Mann-Whitney U test for continuous variables and Fisher's exact test for categorical variables. The primary associations of interest were between serum T3 and APACHE II score and NT-proBNP; associations with other severity markers were exploratory, assessed using Spearman's rank correlation without adjustment for multiplicity.

Results:

Among 66 enrolled patients, 39 (59.1%) had LT3S. The LT3S group had significantly higher APACHE II scores (12.8 ± 4.2 vs. 9.6 ± 3.5; p = 0.003) and higher NT-proBNP (median 10,042 vs. 4,153 pg/mL; p = 0.036) than the normal T3 group. Continuous serum T3 correlated modestly and inversely with APACHE II score (r = − 0.29, p = 0.017) and NT-proBNP (r = − 0.29, p = 0.020), and positively with haemoglobin (r = 0.25, p = 0.042). T3 also correlated with hospital length of stay (r = − 0.25, p = 0.045) and age (r = − 0.26, p = 0.032). No significant correlation was found with left ventricular ejection fraction, serum creatinine, NYHA class, or ICU length of stay. One in-hospital death occurred during the study period, precluding meaningful mortality modelling.

Conclusion:

Lower serum total T3 measured within 6 hours of Emergency Department presentation was modestly associated with APACHE II score and NT-proBNP in patients with acute heart failure, with additional

exploratory associations with other severity-related variables. Only one in-hospital death occurred, precluding assessment of T3 as a predictor of mortality. These findings support T3 as an exploratory correlate of illness severity rather than a validated prognostic biomarker. Larger multicentre studies with longer-term follow-up and serial T3 measurements are required.

Introduction

Acute heart failure (AHF) is a complex syndrome arising from structural or functional cardiac impairment that prevents adequate ventricular filling or ejection (1). It remains a leading global contributor to cardiovascular morbidity and mortality, particularly among older adults with multiple comorbidities such as diabetes, hypertension, and ischaemic heart disease, and is one of the most frequent causes of emergency hospital admission, associated with high in-hospital mortality, prolonged ICU stays, and substantial resource utilisation (23).

In low- and middle-income countries such as India, the burden of AHF is substantial amid demographic transitions and a rising prevalence of cardiovascular risk factors; the Trivandrum Heart Failure Registry has reported substantial in-hospital mortality, underscoring the need for accessible markers that may complement established measures of illness severity (24).

Thyroid hormones play a central role in cardiovascular homeostasis under both physiological and pathological conditions (14, 21). More than 80% of circulating triiodothyronine (T3) originates from peripheral conversion of thyroxine (T4) rather than direct thyroidal secretion (12). T3 acts through genomic pathways, regulating transcription of cardiac contractile genes, and through non-genomic effects on ion channels and vascular tone, thereby enhancing myocardial contractility and reducing systemic vascular resistance (14, 21). During critical illness and acute cardiac dysfunction, patients frequently develop non-thyroidal illness syndrome (NTIS), historically termed ‘euthyroid sick syndrome’, characterised by low T3 with relatively preserved TSH (17, 18); in heart failure patients who are otherwise clinically euthyroid, T3 falls markedly while TSH remains within normal limits (3, 5). NTIS arises predominantly from reduced peripheral type 1 deiodinase activity, altered hormone binding, and hepatic clearance (17), a process driven by systemic inflammation: elevated circulating cytokines and oxidative stress suppress the hypothalamic-pituitary-thyroid axis and peripheral deiodinases (9, 20), compounded in AHF by hypoxia and tissue congestion. Low T3 syndrome (LT3S) has been linked experimentally to impaired myocardial contractility, increased vascular resistance, and worsened diastolic relaxation (14, 21).

T3 has important cardiovascular effects, including modulation of myocardial contractility and vascular tone (6, 14, 21). During critical illness and acute cardiac dysfunction, NTIS is characterised by reduced T3 with relatively preserved TSH and may result from altered peripheral deiodinase activity, hormone binding, clearance, and inflammatory signalling (17, 18, 20, 33). These mechanisms provide biological plausibility for an association between T3 concentrations and the physiological derangement captured by established severity measures, although they do not establish that T3 independently determines

clinical outcomes. At the molecular level, these effects involve epigenetic regulation of cardiac gene transcription (7), inhibition of cardiac myocyte apoptosis following short-term T3 exposure in experimental models (8), and antisense-transcript-mediated regulation of thyroid-responsive genes (10).

A growing body of clinical evidence associates LT3S with adverse outcomes across the cardiovascular disease spectrum: in chronic heart failure, low T3 has been linked to advancing age, reduced ejection fraction, and mortality (2); in acute myocardial infarction, it has been associated with adverse cardiovascular outcomes (16); and in acute decompensated states, LT3S has been associated with higher mortality and prolonged hospitalisation (11, 13, 19). However, evidence specifically evaluating total T3 against both APACHE II and NT-proBNP among ED-presenting, ICU-admitted AHF patients in a secondary-care Indian setting remains limited. The present study therefore evaluates the association of admission serum total T3 with established measures of illness severity, with mortality considered only as an exploratory clinical outcome.

Methods

Study Design, Setting, and Ethical Approval

This single-centre, prospective, observational study was conducted over an 18-month period (September 2017 to February 2019) in the Emergency Department and Intensive Care Unit (ICU) of Dr. TMA Pai Hospital, Udupi, a secondary-care teaching hospital affiliated with Manipal Academy of Higher Education, in South India and is reported in accordance with the STROBE guidelines (26). The study protocol received full ethical clearance from the Institutional Ethics Committee (IEC No. MED/2017/232). Written informed consent was obtained from all conscious patients or their legally authorised representatives prior to enrolment.

Inclusion and Exclusion Criteria

Adult patients (aged ≥ 18 years) presenting to the Emergency Department with acute heart failure (AHF), diagnosed by the Principal Investigator using the Framingham Heart Failure Criteria (23), requiring either two major criteria or one major plus two minor criteria, with echocardiography and NT-proBNP used as supportive objective evidence where available, were consecutively evaluated for eligibility and subsequently admitted to the ICU for further management (Fig. 1). Systematic sub-classification into de novo versus decompensated chronic heart failure, or exclusion of ACS-associated presentations, was not performed. Patients were excluded if they had known primary thyroid disorders or were taking thyroid medications; underlying pituitary disease; pregnancy or active lactation; concomitant severe sepsis, end-stage liver disease, or end-stage renal disease; amiodarone therapy; or recent transfer from another ICU.

Sample Size

Patients were consecutively enrolled over the 18-month study period. The original study protocol specified in-hospital mortality as the primary clinical outcome, with the association between serum T3 and illness severity, assessed via APACHE II score and NT-proBNP, as a prespecified secondary objective. However, only one in-hospital death occurred during the study period, precluding meaningful statistical analysis of the primary mortality outcome. The present report therefore focuses on the prespecified secondary objective: the association between serum T3 measured within 6 hours of Emergency Department presentation and established markers of illness severity. No formal a priori sample size calculation was performed specifically for these severity-association analyses; therefore, the findings should be considered exploratory and hypothesis-generating rather than confirmatory.

Data Collection and Laboratory Assessment

Blood samples were obtained in the Emergency Department within 6 hours of presentation. Thyroid function tests (total T3, total T4, TSH) were analysed by chemiluminescent immunoassay in a single NABL-accredited laboratory (T3 reference range: 0.8–2.0 ng/mL). Total T3, rather than free T3, was selected because it is more widely available and affordable in secondary-care laboratories; however, free T3 represents the biologically active fraction and may provide additional information not captured by total T3. NT-proBNP was measured by standardised ELISA. APACHE II scores were calculated according to standard methodology, using the worst physiological values recorded during the first 24 hours of ICU care, by a physician blinded to the thyroid profile. Transthoracic echocardiography was performed by a trained echocardiography technician within 6 hours of presentation, in the Emergency Department or ICU as clinically appropriate, to assess left ventricular ejection fraction (LVEF). Patients were stratified into the LT3S group (total T3 < 0.8 ng/mL) and the normal T3 group (total T3 ≥ 0.8 ng/mL), using the lower limit of the laboratory's normal reference range as the pre-specified cut-off.

Outcomes and Statistical Analysis

The analysis reported here addresses the study's prespecified secondary objective: the association between serum total T3 measured within 6 hours of Emergency Department presentation and illness severity, assessed using APACHE II score and NT-proBNP. Other outcomes assessed were ICU length of stay, total hospital length of stay, requirement for mechanical ventilation, requirement for inotropic/vasopressor support, and in-hospital mortality, the latter analysed on an exploratory basis because only one mortality event occurred. Normality of continuous variables was assessed within each T3 group using the Shapiro-Wilk test; variables normally distributed in both groups (Shapiro-Wilk $p > 0.05$) are expressed as mean ± standard deviation (SD), while variables violating normality in either group ($p \leq 0.05$) are expressed as median with interquartile range (IQR); categorical variables are presented as frequencies and percentages. Group comparisons used the Mann-Whitney U test for continuous variables and Fisher's exact test for categorical variables, given the modest sample size. For continuous variables, 95% confidence intervals for the between-group location shift were calculated using the Hodges-Lehmann estimate, consistent with the Mann-Whitney U test; for categorical variables, 95%

confidence intervals for the risk difference were calculated using the Newcombe method, consistent with Fisher's exact test. Associations between continuous serum T3 and severity markers were assessed using Spearman's rank correlation. Mortality modelling using multivariable logistic regression or ROC/AUC analysis was not undertaken because only one death occurred. No adjustment for multiple comparisons was prespecified because the secondary correlation analyses were exploratory; therefore, nominal p-values should be interpreted cautiously. Statistical significance was defined as a two-sided p-value < 0.05. Analyses were performed using Python (SciPy, statsmodels). All 66 enrolled patients were included in the final analyses, with no loss to follow-up during hospitalisation. No missing data were present for variables included in the primary or secondary analyses. As a sensitivity analysis, given that age contributes to the APACHE II score, a partial correlation between T3 and APACHE II adjusting for age was calculated.

Results

Baseline Patient Characteristics

Over the 18-month study period, 66 patients meeting inclusion criteria for AHF were consecutively enrolled: 39 (59.1%) had total T3 < 0.8 ng/mL (LT3S) and 27 (40.9%) had normal T3 levels. No statistically significant differences were observed in baseline demographics, comorbidities, LVEF, or HFrEF proportion between groups: age (70.5 ± 9.9 vs. 66.7 ± 14.0 years; p = 0.267), sex (48.7% vs. 55.6% male; p = 0.624), hypertension (59.0% vs. 66.7%; p = 0.610), diabetes mellitus (38.5% vs. 37.0%; p = 1.000), ischaemic heart disease (46.2% vs. 55.6%; p = 0.617), LVEF (47.9 ± 10.0% vs. 48.0 ± 10.0%; p = 0.971), and HFrEF (LVEF < 40%: 20.5% vs. 14.8%; p = 0.748).

Thyroid Function and Illness Severity Markers

Serum total T3 (0.61 ± 0.11 vs. 0.95 ± 0.12 ng/mL; p < 0.001) and median T4 (5.81 vs. 7.85 µg/dL; p < 0.001) were significantly lower in the LT3S group, while median TSH did not differ significantly (2.03 vs. 2.44 mIU/L; p = 0.223), consistent with a non-thyroidal illness syndrome pattern rather than primary thyroid dysfunction. The LT3S group had significantly higher APACHE II scores (12.8 ± 4.2 vs. 9.6 ± 3.5; p = 0.003) and higher median NT-proBNP (10,042 vs. 4,153 pg/mL; p = 0.036), and significantly lower haemoglobin (median 11.2 vs. 12.6 g/dL; p = 0.013) (Table 1).

Table 1
Baseline Demographic and Clinical Characteristics by T3 Group

Variable	Low T3 (n = 39)	Normal T3 (n = 27)	p-value	95% CI
Age (years)	70.5 ± 9.9	66.7 ± 14.0	0.267	3.0 [-3.0, 10.0]
Male sex	19 (48.7%)	15 (55.6%)	0.624	-6.8% [-29.3%, 16.8%]
Hypertension	23 (59.0%)	18 (66.7%)	0.610	-7.7% [-29.1%, 15.7%]
Diabetes mellitus	15 (38.5%)	10 (37.0%)	1.000	7.7% [-15.7%, 29.1%]
IHD	18 (46.2%)	15 (55.6%)	0.617	-17.7% [-38.9%, 4.6%]
Serum total T3 (ng/mL)	0.61 ± 0.11	0.95 ± 0.12	< 0.001***	-0.32 [-0.37, -0.26]
Serum total T4 (µg/dL), median [IQR]	5.81 [4.83–7.39]	7.85 [7.16–9.12]	< 0.001***	-1.99 [-2.80, -1.14]
TSH (mIU/L), median [IQR]	2.03 [1.30–3.21]	2.44 [1.66–3.80]	0.223	-0.38 [-1.04, 0.24]
APACHE II Score	12.8 ± 4.2	9.6 ± 3.5	0.003**	3.0 [1.0, 5.0]
NT-proBNP (pg/mL), median [IQR]	10,042 [2,954–16,032]	4,153 [2,142–8,468]	0.036*	3,433 [176, 8,813]
LVEF (%)	47.9 ± 10.0	48.0 ± 10.0	0.971	0.0 [-6.0, 5.0]
HFrEF (LVEF < 40%)	8 (20.5%)	4 (14.8%)	0.748	5.7% [-14.5%, 23.2%]
Serum creatinine (mg/dL), median [IQR]	1.10 [0.80–1.35]	1.00 [0.80–1.25]	0.299	0.10 [-0.10, 0.32]
Haemoglobin (g/dL), median [IQR]	11.2 [9.9–12.7]	12.6 [11.6–13.4]	0.013*	-1.40 [-2.40, -0.30]

* p < 0.05; ** p < 0.01; *** p < 0.001. P-values from Mann-Whitney U test (continuous) and Fisher's exact test (categorical). LVEF determined from complete echocardiographic ejection fraction data for all 66 patients. Normality was assessed by Shapiro-Wilk testing within each T3 group; T4, TSH, and serum creatinine violated normality in at least one group and are therefore presented as median [IQR] rather than mean ± SD. Serum total T3 differs between groups by definition, since T3 level was the variable used to define group membership. For continuous variables, the reported 95% CI represents the Hodges-Lehmann between-group location shift; for categorical variables, it represents the risk difference.

Correlation of Continuous Serum T3 with Severity Markers

Continuous serum T3 correlated significantly and negatively with the two primary severity measures, APACHE II score (Spearman r = − 0.293, p = 0.017) and NT-proBNP (Spearman r = − 0.285, p = 0.020). In an age-adjusted sensitivity analysis, the inverse association between T3 and APACHE II attenuated and was no longer statistically significant (partial Spearman correlation r = − 0.237, p = 0.057). Exploratory secondary correlations showed positive association with haemoglobin (r = 0.251, p = 0.042) and negative associations with hospital length of stay (r = − 0.247, p = 0.045) and age (r = − 0.264, p = 0.032). No significant correlation was observed with left ventricular ejection fraction, serum creatinine, NYHA class, or ICU length of stay. Given the number of secondary correlations examined and the absence of multiplicity adjustment, these nominal p-values should be interpreted cautiously.

Table 2
Correlation of Continuous Serum T3 with Illness Severity Markers

Variable (n = 66)	Correlation coefficient	Method	p-value	95% CI
APACHE II Score	r = − 0.293	Spearman	0.017*	[-0.500, -0.055]
NT-proBNP	r = − 0.285	Spearman	0.020*	[-0.493, -0.046]
Haemoglobin	r = 0.251	Spearman	0.042*	[0.010, 0.465]
Age	r = − 0.264	Spearman	0.032*	[-0.476, -0.023]
Hospital length of stay	r = − 0.247	Spearman	0.045*	[-0.461, -0.005]
LVEF	r = 0.014	Spearman	0.911	[-0.229, 0.255]
Serum creatinine	r = − 0.172	Spearman	0.167	[-0.397, 0.073]
NYHA class	r = 0.078	Spearman	0.534	[-0.167, 0.314]
ICU length of stay	r = − 0.150	Spearman	0.228	[-0.378, 0.095]

* p < 0.05. Spearman's rank correlation used uniformly for all variables. Correlations with APACHE II score and NT-proBNP represented the two primary severity associations; the remaining correlations were exploratory. No multiplicity adjustment was applied to the exploratory analyses, and nominal p-values should therefore be interpreted cautiously.

Short-Term Clinical Outcomes

Hospital length of stay was numerically longer in the LT3S group (8.0 ± 3.3 vs. 7.0 ± 2.6 days) though this difference did not reach statistical significance (p = 0.149). Median ICU length of stay was similar between groups (3.00 [3.00–4.50] vs. 3.00 [3.00–4.00] days; p = 0.962). Requirement for mechanical ventilation (30.8% vs. 33.3%; p = 1.000) and inotropic/vasopressor support (10.3% vs. 18.5%; p = 0.469) did not differ significantly between groups. One in-hospital death occurred during the study period, in a patient from the LT3S group (1/39, 2.6% vs. 0/27, 0.0%; p = 1.000) (Table 3). Given this single mortality event, formal multivariable or ROC-based analysis of T3 as a predictor of in-hospital mortality was not

undertaken, as such analyses require substantially more events to yield stable and interpretable estimates.

Table 3
Short-Term Clinical Outcomes by Serum T3 Group

Outcome	Low T3 (n = 39)	Normal T3 (n = 27)	p-value	95% CI
Total hospital length of stay (days)	8.0 ± 3.3	7.0 ± 2.6	0.149	1.0 [0.0, 3.0]
ICU length of stay (days), median [IQR]	3.00 [3.00–4.50]	3.00 [3.00–4.00]	0.962	0.0 [-1.0, 1.0]
Requirement for mechanical ventilation	12 (30.8%)	9 (33.3%)	1.000	-2.6% [-25.0%, 18.9%]
Requirement for inotrope/vasopressor support	4 (10.3%)	5 (18.5%)	0.469	-8.3% [-27.5%, 8.6%]
In-hospital mortality	1 (2.6%)	0 (0.0%)	1.000	2.6% [-10.1%, 13.2%]

P-values from Mann-Whitney U test (continuous) and Fisher's exact test (categorical). ICU length of stay violated normality (Shapiro-Wilk) in both T3 groups and is presented as median [IQR] rather than mean ± SD. Only one in-hospital death occurred during the study period; formal predictive modelling of mortality was not undertaken because the event rate was insufficient.

Discussion

This prospective observational study found that LT3S, present in 59.1% of ICU-admitted AHF patients, was associated with higher APACHE II scores and NT-proBNP and lower haemoglobin at early presentation. Continuous T3 also showed modest correlations with APACHE II, NT-proBNP, haemoglobin, age, and hospital length of stay. Only one in-hospital death occurred, precluding assessment of T3 as a mortality predictor. The findings therefore support an association between T3 and established severity markers rather than independent prognostic value.

Low T3 syndrome as a marker of illness severity

These findings are consistent with a growing body of literature suggesting NTIS more consistently reflects physiological derangement than it independently predicts short-term mortality. Zhao et al. followed 594 patients with acute decompensated heart failure and found LT3S significantly associated with 1-year mortality (HR 1.85, 95% CI 1.21–2.82, P = 0.005) but not in-hospital mortality (adjusted HR 1.58, P = 0.290) (11). A very recent registry study of 1,568 HFmrEF patients similarly found isolated LT3S independently predicted long-term (30-month) mortality (HR 1.594, 95% CI 1.185–2.145, P = 0.002) but not rehospitalisation (36) — reinforcing that LT3S's prognostic signal in heart failure appears strongest over longer follow-up than assessed here. In a 1,790-patient ICU cohort, NTIS predicted mortality

univariately but was not retained independently after adjustment for ventilation duration, kidney injury, and sepsis (27); a comparably sized (n = 109) ICU study concluded NTIS “may serve as a biomarker of critical illness severity rather than an independent predictor of mortality” (28), directly supporting the present findings.

Reconciling conflicting reports in the literature

Other studies report T3/FT3 discriminating mortality comparably to APACHE II. Wang et al. (n = 480 ICU patients) found FT3’s AUC (0.762) approached APACHE II’s (0.829) and remained independently predictive, correlating with NT-proBNP (r = − 0.344) and CRP (r = − 0.408) (29). Thilak et al. (257 South Indian ICU patients, 47 deaths) reported T3 AUC 0.811, nearly matching APACHE II’s 0.858, with T3-APACHE II correlation (r = − 0.448) (19). These studies recorded substantially more mortality events than the present cohort. The single death observed here makes the present study unable to determine whether a biological association between T3 and mortality exists. Because age contributes to the APACHE II score and was also inversely correlated with T3 in this cohort, the age-adjusted attenuation of the T3–APACHE II association (Results) indicates that part of the observed relationship may reflect age-related variation rather than a fully independent association.

Methodological implications of very few outcome events

The limited number of outcome events has important methodological implications. Statistical literature has shown that sparse outcome events can produce unstable and biased estimates in logistic regression models (25, 30, 31). With only one death across 66 patients, the present cohort was therefore unsuitable for reliable multivariable mortality modelling or ROC/AUC analysis. This is a limitation of the observed event rate and should not be interpreted as evidence against prognostic associations that may be detectable in larger cohorts.

The role of serial, rather than single-timepoint, T3 measurement

Measuring T3 trajectory, rather than a single value, may be more informative. Seven et al. found baseline free T3 unrelated to 30-day mortality in 74 ICU patients, whereas its 48–72-hour change (ΔT3) was strongly predictive, with APACHE II plus ΔT3 reaching AUC 0.921 versus 0.861 for APACHE II alone (32) — suggesting a single early measurement, as used here, may be an inherently weaker prognostic signal.

Mechanistic basis for the severity association

The correlation between low T3 and distinct severity markers, which are themselves likely correlated rather than statistically independent, is biologically compatible with NTIS as a downstream response to systemic inflammation. Cytokine-mediated changes in deiodinase activity and thyroid hormone metabolism may contribute to reduced circulating T3 during acute illness (17, 18, 33), although these mechanisms were not directly measured in the present study. Such mechanisms may contribute to the physiological derangements reflected by APACHE II and NT-proBNP, but the present observational data cannot establish a causal pathway.

Clinical implications in secondary-care settings

Serum total T3 is relatively inexpensive and technically simple to measure in secondary-care laboratories, supporting its potential as an accessible adjunctive correlate of illness severity. However, this study does not establish incremental clinical utility, does not support T3 as a substitute for NT-proBNP, and does not establish independent mortality prediction. Its findings should therefore be interpreted as hypothesis-generating associations requiring validation in larger cohorts, consistent with similar regional precedents in South Indian ICU populations (34, 35).

Limitations

This study has several important limitations. First, only one in-hospital death occurred during the study period; the original hypothesis regarding T3's prognostic value for mortality could not be meaningfully tested, and formal predictive modelling was not undertaken. Second, the modest sample size (n = 66) limits precision even for the cross-sectional associations reported here, and the observed correlations ($r \approx 0.25–0.29$), while nominally significant, are modest. Third, all participants were AHF patients who required ICU admission; therefore, the cohort represents an ICU-selected population and the findings should not be extrapolated to all patients presenting to the Emergency Department with AHF. Fourth, the single-centre secondary-care design may limit generalisability to tertiary academic ICU settings with different case-mix and referral patterns. Fifth, this study measured total T3, rather than free T3 or reverse T3 (rT3), at a single admission timepoint; total T3 was chosen for its affordability and availability, but free T3 is the biologically active fraction and may carry additional information, while serial measurement may be more informative than a single value. Sixth, as an observational study, residual confounding cannot be excluded; although medications and comorbidities were recorded for each patient, the sample size did not permit formal statistical adjustment for their potential confounding effect on the T3-severity association, and nutritional status and comorbidity severity not fully captured by APACHE II remain unmeasured. Seventh, ongoing debate also surrounds whether exogenous T3 supplementation improves outcomes in LT3S; intravenous T3 has shown haemodynamic benefit in small trials (4), but its routine use remains contested (15, 22), and this study's design does not address whether correcting low T3 would alter illness trajectory. Eighth, multiple secondary correlations were examined without multiplicity adjustment, increasing the possibility of type I error; these findings should therefore be considered exploratory. Finally, data were collected in 2017–2019. Although the pathophysiology of NTIS and the assay methodology remain relevant, the temporal and single-centre nature of the dataset limits contemporary generalisability. Larger multicentre studies with longer-term follow-up and serial T3 measurement are needed to determine whether T3 provides independent prognostic information beyond established severity measures.

Conclusion

Lower serum total T3 measured within 6 hours of Emergency Department presentation was modestly associated with established markers of illness severity in patients with acute heart failure, including APACHE II score and NT-proBNP, with additional exploratory associations with haemoglobin, age, and

hospital length of stay. Only one in-hospital death occurred during the study period, precluding assessment of T3 as a predictor of in-hospital mortality. Given the modest effect sizes, exploratory secondary analyses, absence of multiplicity adjustment, and ICU-selected single-centre population, these findings should be interpreted as associations rather than evidence of independent prognostic value. Serum total T3 may warrant further evaluation as an accessible adjunctive correlate of illness severity, but larger multicentre studies with serial measurements and longer-term outcomes are required before clinical utility or prognostic value can be established.

Abbreviations

Abbreviation
Full Form
AHF
Acute Heart Failure
APACHE II
Acute Physiology and Chronic Health Evaluation II
AUC
Area Under the Curve
CI
Confidence Interval
ELISA
Enzyme-Linked Immunosorbent Assay
FT3
Free Triiodothyronine
HFmrEF
Heart Failure with Mildly Reduced Ejection Fraction
HFrEF
Heart Failure with Reduced Ejection Fraction
HR
Hazard Ratio
ICU
Intensive Care Unit
IEC
Institutional Ethics Committee
IHD
Ischaemic Heart Disease
IQR
Interquartile Range
LMIC(s)
Low- and Middle-Income Country/Countries

LT3S
Low T3 Syndrome
LVEF
Left Ventricular Ejection Fraction
MICU
Medical Intensive Care Unit
NABL
National Accreditation Board for Testing and Calibration Laboratories
NT-proBNP
N-terminal pro-B-type Natriuretic Peptide
NTIS
Non-Thyroidal Illness Syndrome
NYHA
New York Heart Association (functional class)
ROC
Receiver Operating Characteristic
SD
Standard Deviation
STROBE
Strengthening the Reporting of Observational Studies in Epidemiology
T3
Triiodothyronine
T4
Thyroxine
TSH
Thyroid-Stimulating Hormone
VIF
Variance Inflation Factor

Declarations

Ethical Approval and consent to participate

This prospective observational study received approval from the Institutional Ethics Committee (IEC No. MED/2017/232) prior to enrolment. Written informed consent was obtained from all conscious patients or their legally authorised representatives prior to enrolment, in accordance with the ethical principles of the Declaration of Helsinki. Confidentiality of patient information was strictly maintained throughout. Clinical trial number: Not applicable

Consent for Publication

Not Applicable

Data sharing statement

All study data are available upon request from the corresponding author, other than the supplementary material provided.

Declaration of Conflict interest statement

The authors report there are no competing interests to declare.

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Author contributions statement

D.D.P. and S.N.S. contributed to the conceptualization, study design, and methodology development.

D.D.P. performed data collection and data entry.

D.D.P., N.S. and S.N.S. conducted data curation, formal data analysis and statistical interpretation.

D.D.P. and S.T.S. wrote the main manuscript text and prepared the tables and figures.

D.D.P., S.A.K., S.T.S., N.S., and S.N.S. contributed to critical revision of the manuscript for important intellectual content.

Author Contribution

D.D.P. and S.N.S. contributed to the conceptualization, study design, and methodology development.D.D.P. performed data collection and data entry.D.D.P., N.S. and S.N.S. conducted data curation, formal data analysis and statistical interpretation.D.D.P. and S.T.S. wrote the main manuscript text and prepared the tables and figures.D.D.P., S.A.K., S.T.S., N.S., and S.N.S. contributed to critical revision of the manuscript for important intellectual content.

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Figures

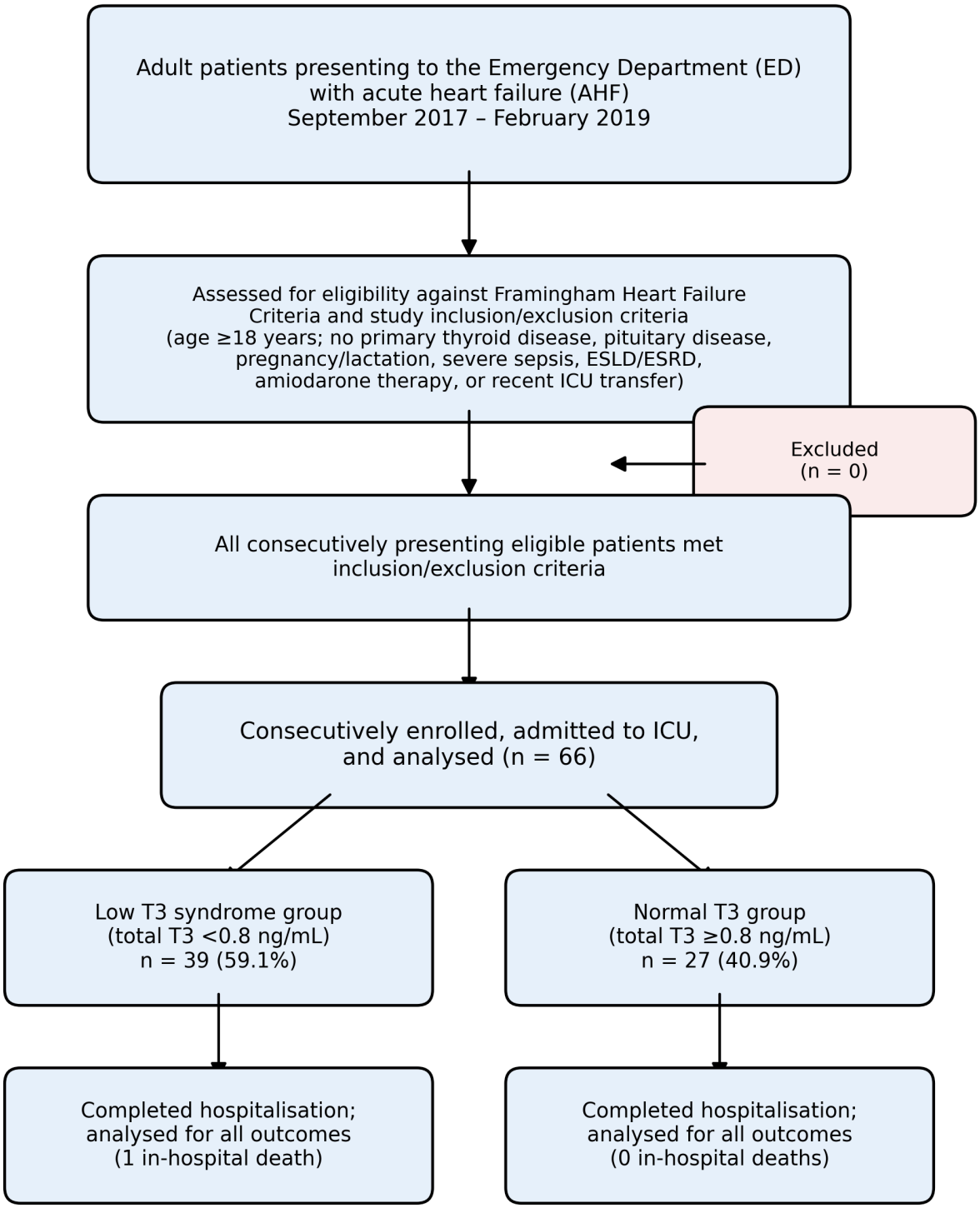


Figure 1

Flow of participants through the study. All consecutively presenting patients meeting the Framingham Heart Failure Criteria during the 18-month enrolment period satisfied inclusion/exclusion criteria; no patients were excluded. All 66 enrolled patients completed hospitalisation and were included in the final analysis (Low T3 syndrome group, n=39; Normal T3 group, n=27).