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Orıgınal Article

Non-thyroidal Illness in Children with Congestive Heart Failure

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What is already known?
• Sick euthyroid state is seen in critical patients that adversely affects outcomes.
• Thyroid hormones affect cardiac function and contractility.

What this study adds?
• Sick euthyroid state was seen in 46% children with congestive heart failure.
• Raised brain-natriurteic peptide levels (marker of heart failure) significantly affected low free T3 levels • A free T3/ reverse T3 ratio of <1.86 pg/ng predicted mortality.

Abstract
Objectives: To estimate the proportion and risk factors of non-thyroidal illness (NTI) in children with congenital heart disease (CHD) with congestive heart failure(CHF).
Methods*:* This study enrolled children (6 weeks to 60 months age) with CHD and CHF. The clinical profile and disease severity using Pediatric Early Warning Score (PEWS) was recorded. Baseline blood samples were taken within 24hours of hospitalization and evaluated for fT3, fT4, TSH, NT pro-Brain natriuretic peptide (NT pro-BNP) and reverseT3.
Results*:* A total of 80 (64 acyanotic CHD) children of median (IQR) age 5 (2.5, 8.0) months were enrolled. NTI was seen in 37 (46%)- 27 with low fT3 levels. The proportion of NTI was maximum in children with severe disease (20/30), than moderate (4/9) or mild disease (13/41); p=0.018. Ten (27%) patients with NTI expired as compared to 2 (4.7%) without NTI with unadjusted odds ratio (95% CI) 7.593(1.54, 37.38); p-value=0.006. After adjusting for NTI, shock and NT-pro-BNP levels, PEWS was the only significant predictor of mortality (OR 1.41, 95% CI 1.03, 1.92; p=0.032).Linear regression for fT3 showed significant relation with log NT-BNP [beta -3.541, (95% CI -1.387, -0.388)] and with TSH [beta 2.652 (95%CI 0.054, 0.383)]. The cutoff (AUC, 95%CI) that predicted mortality were fT4 <14.5 pmol/L (0.737, 0.60, 0.88), fT3/rT3 index <1.86 pg/ng (0.284, 0.129, 0.438) and NT pro-BNP >3725 pg/mL (0.702; 0.53, 0.88).
Conclusion*:* NTI was seen in a significant proportion of children with CHD and CHF. Free T3 level was significantly affected with NT-BNP levels (severity of CHF).
Keywords: Non-thyroidal illness, free T3, reverse T3, NT pro-BNP and Pediatric early warning score

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INTRODUCTION

Cardiovascular structure and function in the pediatric age group is affected by changes in body size, metabolic demands, as well as hormonal effects. Effect of thyroid hormones (TH) on adult cardiovascular system (CVS) has been studied widely. The CVS is a well-known target for TH as is exhibited by its profound effects on cardiac contractility, heart rate, systemic vascular resistance, ventricular mass and body's blood volume [1,2]. Cardiomyocytes express thyroid receptors (TRα and TRβ). The genetic transcription of contractile proteins of myosin heavy chains is dependent on TH in fetal and postnatal life suggesting their association [3].
Non-thyroidal illness (NTI) (also known as sick euthyroid syndrome), is frequently reported in critically sick patients. It is postulated to be a state of adaptive response where the body adapts to assume a low metabolic state to conserve energy, like calorie restriction in acute illness. During prolonged illness, this state represents the abnormal effect of illness on the hypothalamic-pituitary axis where there is low generation of TH. Low free tri-iodothyronine (fT3) results from reduced enzyme activity of 5' monodeiodinase (type 1 and 2) which is responsible for peripheral conversion of tetra-iodothyronine (T4) to T3 [1,4].There is an increase in activity of deiodinase type 3 that increases the generation of reverse T3 (3,3',5'-triiodothyronine or rT3), the inactive form, and also suppression of release of thyrotropin releasing hormone (TRH) from the pituitary in prolonged disease states [5,6].
Overall, sick euthyroid state is associated with poor disease outcomes and mortality. An association between lower fT3 level, raised rT3 level and lower cardiac ejection fraction has been seen in patients with acute myocardial infarction, heart failure and after coronary artery bypass surgery [1]. A few studies have reported occurrence of NTI in critically sick children that was associated with a worse prognosis [4,7-9].Congenital heart diseases (CHD) are one of the most common cardiovascular diseases in children that usually present with congestive heart failure (CHF). The children with CHF are usually sick at presentation and at an increased risk of repeated hospitalizations and medical follow-up. The associated hepatic congestion in CHF may cause an inhibition of hepatic deiodinase type 1 with resultant lower T3 levels [8]. A suboptimal thyroid status in children with CHD and CHF can inturn compromise the cardiac function further. Poorly controlled CHF with decompensated left ventricular hypertrophy and low cardiac output can further decrease the cardiac TH than those with preserved cardiac output in animal model [10].
The primary objective of this study was to evaluate the proportion of children with CHD and CHF with non-thyroidal illness. We also aimed to study the association of TH with cardiac contractility (ejection fraction) and clinical outcomes like duration of hospitalization and mortality.

METHODS

This observational study was conducted at the Department of Pediatrics and Cardiology of a large tertiary care public hospital from July 2021 till June 2022 after approval of the Institutional ethics committee. Written parental consent was taken before enrollment. The study protocol was in agreement with the Declaration of Helsinki for conduct of research and registered under clinical trials registry with registration number CTRI/2021/03/032417.

Children between age group of 6 weeks to 60 months diagnosed with CHD **(**cyanotic or acyanotic heart disease) with CHF were eligible for inclusion. Children with past history of thyroid disease (congenital hypothyroidism) or history of intake of thyroxine in last 3months, congenital anomalies like Down Syndrome, Turner syndrome or Williams-Beuren syndrome, children with history of birth asphyxia, cardiomyopathy or myocarditis were excluded. All eligible children were enrolled within 24 hours of hospitalization.

SAMPLE SIZE:

Sample size calculation was done using Open Epi software with a proportion of non-thyroidal illness as 24.5% in patients with underlying heart failure [1]. A sample size of 72 was calculated with 5% alpha error and power of 80%. We recruited a total of 80 children for the study.

The demographical details, birth and developmental history and feeding history were elicited and recorded. The age of diagnosis of CHD, disease progression, details of prior hospitalization (if any) and treatment history for decongestants or other drugs were noted. Children with CHF who were controlled on medications and those who presented in decompensated CHF were both enrolled. The vitals including temperature, heart rate, respiratory rate and blood pressure were measured followed by physical examination including anthropometry. WHO 2006 standards were used to interpret anthropometry in terms of standard deviation scores (SDS) [11]. Non-invasive blood pressure was measured as per standard protocol and interpreted as per American Academy of Pediatrics (AAP) [12]. Cardiac lesions were further classified as acyanotic congenital heart disease (ACHD) or cyanotic congenital heart disease (CCHD) based on clinical examination.

A prognostic clinical scoring was done at hospitalization by using Pediatric Early Warning Score (PEWS) [13] The score recorded a value from 0 to 3 (0 for best and 3 for worst) for each of the three variables- behaviour, cardiovascular and respiratory. As per PEWS, patients were categorized as mild, moderate or severe sickness for a score of 0-3, 4-6 score and 7-9, respectively. The outcome of all children was recorded till discharge or death. The duration of hospitalization and oxygen need were also recorded in total days. A venous blood sample was collected and processed for biochemical investigations. One serum aliquot was separated and stored at -80ºC for thyroid functions. Liver function test, serum creatinine and C- reactive protein (CRP) were measured at the time of enrolment. The liver function tests and serum creatinine was measured on an autoanalyzer Vitros 5600. CRP was measured using ELISA with normal range <5 mg/L. A three-times raise in CRP was taken suggestive of infection and was evaluated further for sepsis.

The thyroid stimulating hormone (TSH), fT3, fT4was processed on a weekly basis and reverse T3 (rT3) level was processed as a single batch by Electrochemiluminescence (ECLIA). Non-thyroidal illness (or sick euthyroid illness) was defined as low T3 and/or low T4 with normal TSH values and elevated rT3 levels. Hypothyroidism was defined as elevated TSH (>10mIU/L) with low fT4. Subclinical hypothyroidism was defined as elevated TSH between 5-10 mIU/L with normal fT4 values. The normal ranges were TSH 0.46-4.68 mIU/L, free T3 4.26-8.10 pmol/L, free T4 10-22.8 pmol/L, rT3 0.06-0.76 ng/mL (<250pg/mL). The fT3/rT3 index (pg/ng) was mathematically derived by converting fT3 pmol/L to pg/mL (multiply by 0.651) and ratio was calculated rT3 (in ng/mL). The intra and inter-assay coefficient of variation (CV) for fT4 was 1.7-5.7% and 3-10.7%, fT3 1.1-3% and 1.9-8.2% and TSH 1.5-4.2% and 2.4-6.3%, respectively.

One mL of blood sample for serum NT pro-BNP was measured within 24hours of collection by Electrochemiluminescence (ECLIA) (maximum storage limit at 2-8ºC was 3days). The normal range for serum NT pro-BNP (children > one-month age) was 20-40 pg/mL [14]. NTI was classified as NTI-1 or Low T3 syndrome, in which there is decrease total or free T3 with normal T4 and TSH level and NTI-2 or Low T4 syndrome, with significant fall in both T3 and T4 with normal or low TSH level [15].

A plain chest radiograph was done at enrolment to document the cardiac size and any other lung abnormality. A standard electrocardiogram was done at the bedside of the patients after standard calibration and abnormalities recorded. Echocardiography was done using Philip's EPIQ CVX ultrasound machine at a frequency of 7-12 Hz in M mode to measure ejection fraction once the child was stable for transport. Ejection fraction (EF) was defined as percentage of blood volume ejected per cardiac cycle. EF was calculated using Simpson's biplane method and the formula used EF = (EDV-ESV)/EDV or EF = SV/EDV. (EF= ejection fraction, EDV= end diastolic volume, ESV= end systolic volume, SV = stroke volume).

STATISTICAL ANALYSIS

Data were entered in Microsoft Excel and were analyzed using SPSS 25.0 Software. The normality of continuous variables was checked by using Kolmogorov-Smironov test. The categorical variables were described as frequencies and proportions, median (IQR) and mean (SD) were calculated for baseline characteristics like age, growth parameters, biochemical parameters. The continuous variables were compared using *t*-test or Mann Whitney U test. Parameters between three categories of PEWS were compared using ANOVA or Kruskal Wallis test (for non-parametric data). Proportions for those with and without non-thyroidal illness were compared by Chi square test or Fisher's exact test. Odds ratio (OR) (95% CI) was calculated to predict mortality with categorical risk factors (sex, type of CHD, previous hospitalization, failure to thrive, NTI, shock and PEWS category). Binary logistic regression analysis was used using enter and forward selection method to estimate the risk of mortality based on covariates. NT-pro-BNP levels were transformed into logarithmic scale for regression analysis. Free T3/ rT3 index (pg/ng) was calculated by dividing free T3 levels (pmol/L converted to pg/mL by multiplying value by 0.651) with rT3 levels. The correlation between continuous variables was done using Spearman's rank correlation coefficient (*r*) for non-parametric variables. Multiple linear regression (Stepwise) was used for fT3 as dependent and other variables as independent (TSH, NT pro-BNP, PEWS score); fT4 and rT3 were not considered independent for fT3 levels and not included. Receiver operating curve was constructed to measure cut off points for serum NT-pro BNP, fT4 and fT3/rT3 index to predict mortality. A p value less than 0.05 was taken as significant.

RESULTS

A total of 122 patients were screened during the study period, out of whom 42 patients were excluded (26 had Down syndrome, 8 Down phenotype, 1 Turner syndrome, 3 dysmorphism with renal abnormalities, 4 had primary hypothyroidism who were on thyroxine treatment). A total of 80 (49 males) children were enrolled of whom 64 (80%) had acyanotic heart disease. The median (IQR) age was 5 (2.5, 8) months and age at diagnosis was 2.25 (1.5,4) months. Feeding difficulty and poor weight gain were seen in 57(71.3%), and 52(65%), respectively with median (IQR) weight-for-age Z score -3.3 (-4.56, -2.21) and weight-for-length Z score -3.02 (-4.03, -1.38). Sixteen children with cyanotic congenital heart disease (CCHD) and three children with ACHD and severe pulmonary hypertension had cyanosis. As per PEWS, 41(50%) children had mild, 9(11.3%) had moderate and 30(38.7%) had severe disease at hospitalization; with shock in 12 (15%) children. Elevated CRP (more than three times) was seen in 12 children one of whom also had septic shock.

The comparison of biochemical parameters as per disease severity is shown in **Table I.**A total of 37 (46.25%) patients had NTI; 27 (33.8%) had NTI-1 and 10 (12.4%) had NTI-2.The dispersion of fT3, fT4, rT3 and TSH levels as per disease severity in those with and without SES is shown in **Figure 1A, 1B, 1C and 1D** respectively.

Table II shows the comparison of clinical and laboratory parameters in children with or without NTI. Only 3/12 children with elevated CRP had NTI. Similarly, 9/12 children with shock had NTI with an odds ratio of 4.286 (95% CI 1.06,17.23) of developing NTI (p-value 0.031). Logistic regression was performed for predicting mortality with a model based on variables as disease severity (PEWS), shock, rT3 levels, log NT-BNP levels, and presence of NTI. The model (using enter method) explained 44.3% variation in mortality and correctly classified

86.5% of patients with only PEWS as a statistically significant variable (adjusted OR 1.41, 95% CI 1.03, 1.92; p=0.032). PEWS remained as the only significant variable with adjusted odds 1.63 (95% CI 1.25, 2.13; p<0.001) in second model (forward conditioning) (explaining 37.2% of variation).

The fT3 levels showed significant correlation with TSH (*r*=0.461, p<0.001), fT4 (*r*=0.373, p<0.001), rT3 (*r*= -0.488, p<0.001), NT-BNP (*r*= -0.430, p<0.001), and weakly with PEWS (*r*= -0.162, p=0.154). A significant positive correlation was observed between rT3 level and serum NT-pro BNP (*r*= 0.311, p-value =0.007), and a negative correlation with ejection fraction (*r*= -0.233, p-value =0.044). Likewise, serum NT-pro BNP had a significant negative correlation with TSH (*r*= -0.392, p-value <0.001), ejection fraction (*r* = -0.307, p-value= 0.006) and a weaker correlation with fT4 (*r*= -0.082, p-value= 0.475). Multiple linear regression model for fT3 with independent variables PEWS, TSH, log NT-BNP showed statistical significance with TSH and log NT-BNP levels as shown in **Table III**. ly. The statistical values to predict mortality as per the thyroid hormones and serum NT-BNP are shown in **Table IV**.

DISCUSSION

The present study showed a high proportion of NTI in children with CHD and CHF that was seen as low fT3 levels in the majority. The presence of severe disease predicted NTI and risk of mortality more likely.

Non-thyroidal illness has been reported in intensive care settings in pediatric studies [7,8,15] and adult studies [16,17].The pooled prevalence of non-thyroidal illness in adults with CVD was 21.7% (95% CI: 18.4–25.3); and was highest in patients with CHF (24.5%; 95%CI: 18.5–31.7), followed by acute myocardial infarction (18.9%; 95%CI: 10.4– 31.9) and acute coronary syndrome (17.1%, 95%CI: 8.5–31.3) [1]. Non-thyroidal illness has also been reported in children who were critically ill children or had undergone surgical repair of CHD [18]. The present study also reported NTI in a significant proportion of enrolled children with CHF that corroborated with disease severity.

The overall median values of thyroid hormones (fT4 and fT3) and TSH were normal in this study, unlike median rT3 levels which were higher than the normal range, suggesting it to be the earliest affected thyroid parameter in acute sickness. The TSH levels appeared within normal range, but the loss of pulsatile fraction, decreased pulse amplitude, and absence of response to thyrotropin-releasing hormone (TRH) has been reported earlier [19].These parameters were not assessed in the present study but it is likely that these were also affected.

Among natriuretic peptide neurohormones that are secreted as a result of myocardial stretch, NT pro-BNP it is biochemically stable molecule with a longer half-life than BNP, though biologically inactive [20]. The levels increase in CHF and higher levels are associated with poor outcome [14,21].A few studies reported higher serum BNP level in patients with surgical repair for CHD had poorer outcomes [21-23].However, there is limited data on NT pro-BNP levels in children with CHF and association with thyroid functions that were measured in this study. The median NT pro-BNP levels were clearly elevated than normal and higher in those with severe condition as per PEWS score. Serum NT pro-BNP levels showed a significant correlation with fT3 (*r*= -0.430, p-value <0.001), TSH (*r*= -0.392, p-value <0.001) and rT3 (*r*= 0.311, p-value =0.007) in this study, comparable to earlier data [24,25].

Low fT3 levels have been associated with poor outcomes in children and adults with illness in earlier studies [25-27]. The presence of low T3 and raised BNP levels strongly predicted one-year all-cause mortality in acute decompensated CHF in adults, and weakly for in-hospital mortality [28]. Serial trends in thyroid hormone levels in 40 sick children with shock showed a decrease in proportion of low fT3 levels as the sickness improved (82.5% at baseline to 72.5% five days after shock reversal) [29]. The fT3 levels were significantly affected by raised BNP levels in this study (p=0.001), though disease severity remained as the only significant predictor of mortality (odds 1.63). .

Critical illness like infection and inflammation are associated with NTI. A small proportion of children in this study had associated sepsis, and fewer among them had NTI, suggesting the etiology of NTI in the majority as cardiac in origin and less likely infection. A study in critically sick children with haemato-oncological and multisystemic disease concluded fT4 cutoff of 16.6 pmol/L and fT3/rT3 ratio of 11.61 to predict mortality [30].Our study had lower threshold of fT4 (14.5 pmol/L) and fT3/rT3 ratio (1.86 pg/ng) to predict mortality suggesting a lower threshold to monitor sick children with an underlying heart disease.

A few studies have analysed the cardiac response to thyroid supplementation in NTI and have reported contentious results. A meta-analysis did not conclude any beneficial role of either levo-thyroxine or triiodothyronine in NTI [31]. An experimental study with addition of levothyroxine preoperatively in children undergoing cardiac surgery showed a decrease in the inotrope requirement and post-operative cardiac injury [32]. Similar results were also concluded in a meta-analysis of nineteen studies on children undergoing cardiac surgery for CHD with NTI that evaluated the role of preoperative levothyroxine. However, there were no significant improvements in clinical parameters such as duration of hospitalisation, duration of oxygen supplementation, mechanical ventilation support, cardiac index or mortality [33]. There is lack of similar evidence of thyroxine supplementation in non-operative critical illnesses with NTI and this may need evaluation in the future.

This is one of the few studies that have evaluated thyroid hormone axis in children with CHD during hospitalization with consideration to various clinical outcomes and compared with level of sickness. The limited observational period without a prospective follow-up till resolution of NTI was a limitation in this study. The intense severity scoring scales like PRISM/ sequential organ failure assessment (SOFA) were not done due to logistic reasons.

CONCLUSION

Non-thyroidal illness was seen in a significant proportion of children with CHD presenting with CHF. The severity of illness and CHF predicted poorer thyroid function status that was associated with mortality. The study highlights the need to monitor thyroid functions in children with CHD and CHF during acute sickness.

Authorship: AD, SK conceived the idea. BS, AD,BG collected and analyzed data and wrote the initial draft; AA, SK provided critical inputs and revised the manuscript. All authors have read and approve the final draft.

Ethical statement: The study was approved by Institutional Ethics Committee, Maulana Azad Medical College, New Delhi vide letter F No.1/IEC/MAMC/82/10/2020/no.125 dated 14 Jan 2021. It has been registered withclinical trials registry of India (CTRI) with registration number CTRI/2021/03/032417.

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Table I: Clinical and Biochemical parameters as per Pediatric Early Warning Score

Parameters	Mild (n=41)	Moderate (n=9)	Severe (n=30)	p-value
Age (mo)	5(2.5,11)	6(2.5,23)	4.5(2.8,7.0)	0.541
Duration of Stay (d)	8(7,10.75)	9(7.5,12.5)	14(10.75,20.75)	**<0.001**
Duration Oxy (d)	4(2,7)	4(1.5,8)	11(8,19.25)	**<0.001**
WAZ score	-3.36(-4.56, -2.35)	-2.65(-4.03,-1.63)	-3.65(-4.68,-2.74)	0.356
H/LAZ score	-1.85(-2.95, -0.71)	-2.18(-2.88,-0.36)	-1.92(-3.02,-0.98)	0.939
WHZ/WLZ score	-2.96(-3.82, -1.48)	-2.23(-3.91,-0.47)	-3.3(-4.33,-1.40)	0.677
Male*	26(63.4%)	4(44.4%)	19(63.3%)	0.566
ACHD*	34(82.9%)	9(100%)	21(70%)	0.12
Expired*	2(4.8%)	0	10(33.3%)	**0.002**
Past Hospitalisation*	33(80.4%)	8(88.9%)	25(83.3%)	0.896
Shock*	1(2.4%)	0	11(30.55%)	**<0.001**
Sick euthyroid illness*	13(32%)	4(44.4%)	20(66.6%)	**0.018**
fT3 (pmol/L)	4.76(3.75,6.16)	4.9(2.55,6.77)	4.07(3.13,5.43)	0.275
fT4 (pmol/L)	15.3(12.65,23.02)	18.5(17.85,21.75)	14.35(12.17,15.8)	0.059
TSH (IU/mL)	2.38(0.91,3.85)	1.62(0.96,2.26)	1.61(0.43,3.43)	0.453
rT3 (ng/mL)	0.7(0.61,0.91)	0.88(0.72,1.24)	0.85(0.65,1.15)	0.086
fT3/rT3 index (pg/ng)	5.36 (2.74, 6.88)	4.13 (1.91, 5.99)	2.54 (1.51, 3.44)	0.019
NT-pro BNP (pg/mL)	2966(1099,14008)	8396(672,26517)	9690(2721,23515)	0.277
Creatinine (mg/dL)	0.2(0.2,0.3)	0.3(0.25,0.44)	0.3(0.2,0.38)	0.226
CRP (mg/dL)	2(0.61,4.51)	2.13(0.5,5)	3(0.68,9)	0.915
AST (IU/mL)	40.5(34.5,56.75)	37(30,53)	67(38,99.2)	**0.040**
ALT (IU/mL)	33.5(18,50.5)	37(23.5,43)	50(30.25,78.5)	**0.037**
Ejection Fraction (%)	60(55.25,60)	60(55.5,60)	55(50,60)	**0.042**

*Values shown in *numbers (%) for categorical variables or median (IQR) for continuous variables; P-value significant at <0.05; Comparison by *Chi Square test or Kruskal Wallis test; AST Aspartate transaminase; ALT Alanine transaminase; BNP- Brain natriuretic peptide; CRP C-Reactive Protein; fT3- free Triiodothyronine, fT4- free thyroxine; HAZ/LAZ- height or length for age Z score; Duration oxy- duration of oxygenation; rT3 reverse T3; TSH Thyroid stimulating hormone; WHZ/WLZ Weight-for-height/ length Z score; fT3/rT3 index- Units as pg/mL for fT3 and ng/mL for rT3*

Table II. Comparison of clinical and laboratory parameters as per SES status

Parameters	Non-SES (n=43)	SES (n=37)	p-Value
Age (mo)	6(3,11)	4.5(2,6)	0.096
Duration of Stay (d)	9(7,12.25)	11(7.5,15.5)	0.099
Duration of oxygenation (d)	5 (2,10)	8 (4.5,12.5)	**0.012**
PEWS	2 (1.75,3.5)	5 (2,9)	**0.003**
WAZ	-3.25(-4.59, -2.68)	-3.35(-4.47, -2.01)	0.563
HAZ/LAZ	-1.68(-2.75, -0.57)	-1.97(-2.99, -0.91)	0.311
WHZ/WLZ	-3.26(-4.05, -2.04)	-2.57(-3.92, -0.83)	0.108
fT3 (pmol/L)	5.7(4.8,6.8)	3.2(2.7,3.9)	**<0.001**
fT4 (pmol/L)	17.1(14.4,23.6)	14.2(10.95,17)	**0.001**
TSH (mIU/L)	2.66(1.4,4.0)	1.1(0.32,2.2)	**<0.001**
rT3 (ng/mL)	0.66(0.47,0.71)	0.97(0.85,1.26)	**<0.001**

fT3/rT3 index (pg/ng)	6.19 (5.11, 7.72)	2.08 (1.42, 2.72)	**<0.001**
NT-pro BNP (pg/mL)	2786(725,8893)	14900(3345,26392)	**0.001**
Creatinine (mg/dL)	0.2(0.2,0.3)	0.3(0.2,0.39)	0.165
Ejection Fraction (%)	50(55,60)	58(50,60)	0.053

Values shown in median (IQR) for continuous variables, P-value significant at <0.05; Comparison by Mann-Whitney U test; AST Aspartate transaminase; ALT Alanine transaminase; BNP- Brain natriuretic peptide;fT3- free Triiodothyronine, fT4- free thyroxine;HAZ/LAZ- height or length for age Z score; PEWS Pediatric early warning score; rT3 reverse T3; TSH Thyroid stimulating hormone; WHZ/WLZ Weight-for-height/ length Z score; WAZ weight-for age Z score; fT3/rT3 index- Units as pg/mL for fT3 and ng/mL for rT3.

Table III: Linear Regression analysis for low free T3 levels

Model	R square change	Model	Beta	95% CI	P value
1	0.207	Log NT-BNP	-0.455	-1.59, -0.61	<0.001
2	0.275	Log NT-BNP TSH	-3.541 2.652	-1.387, -0.388 0.054, 0.383	0.001 0.010

PEWS excluded during stepwise regression analysis in the model; BNP- Brain natriuretic peptide; fT3- free Triiodothyronine; PEWS- Pediatric early warning score; TSH- Thyroid stimulating hormone

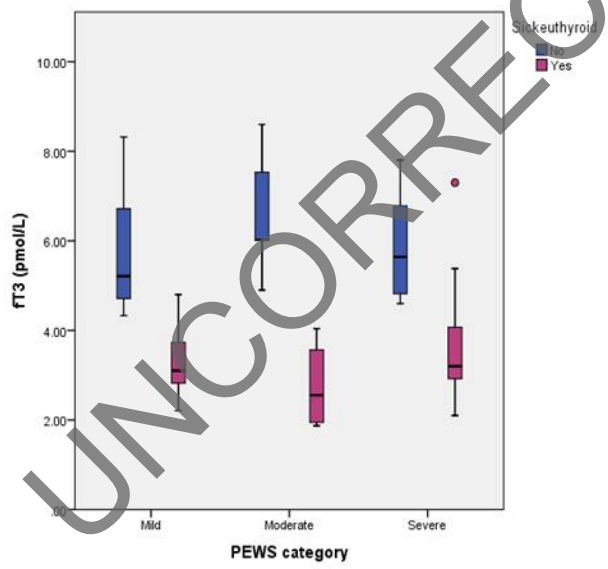
Table IV: Laboratory Cutoffs of Thyroid Hormones To Predict Mortality

Parameter	Value	Sensitivity	Specificity	AUC	95% CI	p value
fT4 (pmol/L)	<14.5	75%	64.2%	0.737	0.60,0.88	**0.009**
fT3 (pmol/L)	<4.15	66.7%	63.2%	0.600	0.41,0.79	0.269
rT3 (ng/mL)	>0.77	83.3%	52.4%	0.741	0.60, 0.88	**0.009**
NT-BNP (pg/mL)	>3725	75%	49.3%	0.702	0.53, 0.88	**0.026**
fT3/rT3 (pg/ng)	<1.861	87.3%	50%	0.284	0.129, 0.438	**0.018**

BNP- Brain natriuretic peptide; fT3- free Triiodothyronine, fT4- free thyroxine; rT3 reverse T3; fT3/rT3 index- Units as pg/mL for fT3 and ng/mL for rT3

Figure 1: Box-Whisker plot showing (A) fT3 levels, (B) fT4 levels, (C) rT3 and (D)TSH levels in non-thyroidal illnesswith severity of PEWS score

A



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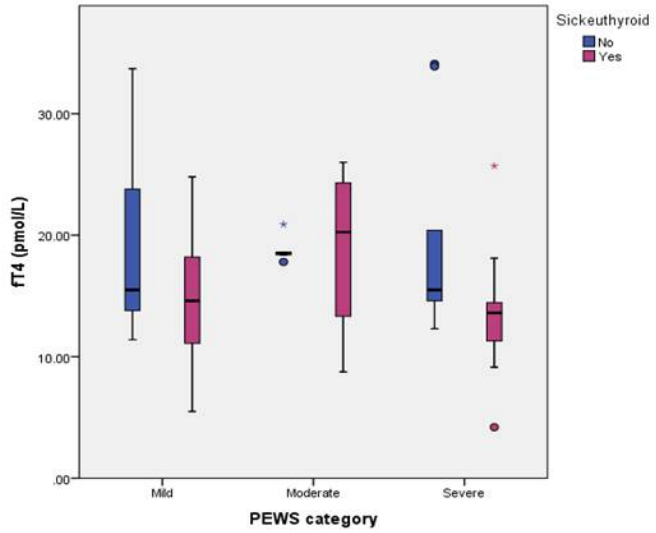

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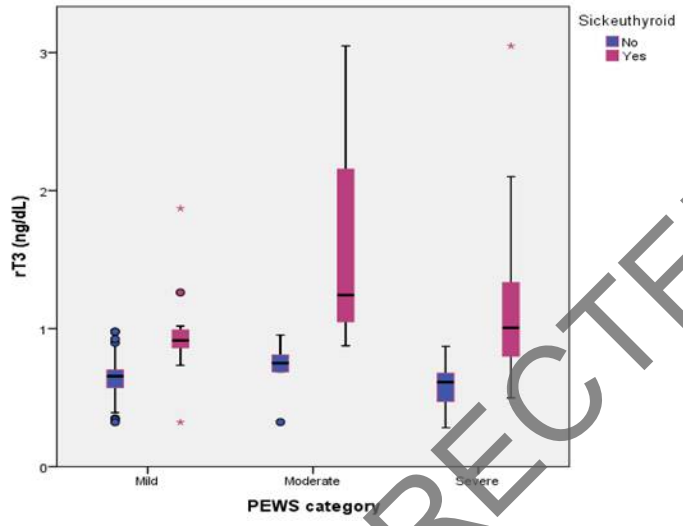

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