The At-Admission fT3/fT4 Ratio Could Predict the Prognosis of Patients Admitted to Surgical ICU

Yehya Shahin Dabour[a]*, Tamer M. Allam[a], Ahmed Abouelgheit Daoud[a]
[a]Department of Anesthesia & ICU, Faculty of Medicine, Benha University, Benha, Egypt.

Abstract

Background: Non-thyroidal illness syndrome (NTIS) is dysregulation of thyroid hormones despite normal thyroid gland function and is diagnosed by low serum triiodothyronine (T3) levels. This condition is associated with caloric deprivation, severe illness and deleteriously affects ICU patients.

Objectives: This study tried to illustrate the relation between thyroid hormonal homeostasis at time of the surgical intensive care unit (SICU)" admission and oncoming complications i.e., in SICU complications rate (CR) and mortality rates (MR).

Patients and methods: Physiological derangement was assessed using the acute physiology and chronic health evaluation II (APACHE II) score. Serum levels of thyroid stimulating hormone (TSH), free and reverse triiodothyronine (fT3 and rT3) and free thyroxine (fT4). The fT3/fT4 ratio was calculated, and ratio <2 suggests the diagnosis of NTIS. Patients were categorized as survivors (SG) and non-survivors (NSG) groups. Study outcomes are the relation between thyroid hormonal levels and patients' outcomes.

Results: The CR and MR were 53.9% and 28.9%, respectively. ICU stay was significantly longer and CR was significantly higher among NSG patients. Mean fT3 levels were significantly lower, while rT3 levels were significantly higher in NSG patients. The mean fT3/fT4 ratio was significantly lower in NSG than in SG patients and 102 patients (44%) had a ratio of <2 with a significant intergroup difference. High APACHE II score, low fT3, and low ratio are the significant predictors for high CR, while low ratio was the highly significant negative predictor for survival.

Conclusion: Low at-admission levels of fT3, low fT3/fT4 ratio and high rT3 levels could predict the vulnerability for getting In-ICU complications and mortality.

Keywords: Non-thyroid illness syndrome; FT3/FT4 ratio; In-ICU complications; In-ICU mortality.

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***Correspondence**: yehyadabour@gmail.com

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Introduction

Major surgical interventions, major/multiple trauma and sepsis that necessitate surgical ICU admission, are associated with altered neuroendocrine axes to ensure survival through optimizing the immune milieu, cardiac function, catabolic phase, and initiation of anabolism to withstand the requirements of tissue repair **(Téblick et al., 2021)**.

Anatomically, the thyroid gland is the largest endocrine gland in the human body and is located anterolateral to the larynx and trachea at the C5-T1 level. TG secret thyroxin (T4) and is de-iodinized peripherally by iodothyronine deiodinases (DIO1 & DIO2) to the tri-iodothyronine (T3) **(Matz et al., 2023)**. Both T3 and T4 are major metabolic regulators, but T3 is 10 times more active than T4 **(Lee and Farwell 2016)**. However, T4 is inactivated by DIO3, which catalyzes the conversion of T4 to the inactive reverse T3 (rT3) **(Ataoglu et al., 2018)**. The ratio between free T3 and free T4 (fT3/fT4) reflects the peripheral thyroid sensitivity, and is an indicator of thyroid hormone metabolic change, which affects the prognosis of specific diseases **(Gao et al., 2021)**.

Non-thyroidal illness syndrome (NTIS) is an ensemble of disturbances in serum thyroid hormone homeostasis that is characterized by a decrease in serum T3 and/or T4 with normal or decreased thyroid-stimulating hormone (TSH) and high levels of rT3 **(Miyahara et al., 2023)**. NTIS is a charming phenomenon because of the relation between low T3 serum levels and morbidity and mortality **(Fliers and Boelen 2021)** in acute illness patients **(Langouche et al., 2019)**, especially older people **(Miao et al., 2023)** and might be initiated by infection or fasting **(Sinkó et al., 2023)**. This study tried to enlighten the neglected impact of disturbed thyroid hormonal milieu on the outcomes of patients admitted to surgical ICU.

Patients and Methods

Design: This prospective observational study was started from Jan 2019 till April 2023

Setting: Departments of Anesthesia & Surgical ICU, and Clinical Pathology, Faculty of Medicine, Benha University in conjunction with multiple private surgical ICUs

Trial registration: The protocol of this current study was approved by the Anesthesia, Pain and ICU departmental committee, Benha University Hospital before starting case collection. The study protocol was freely discussed with patients or their nearest relatives before enrolment and those who accepted to participate in the study were asked to sign a written consent for study participation. At the end of case collection, the study protocol and intervention were approved by the Research Ethic Committee, Benha University with the reference number: RC:4-9-23.

Patients: Considering the design of the study as observational study it depended on collection of all cases admitted to the surgical ICU during the study duration for evaluation for eligibility for inclusion in the study.

Exclusion criteria: The presence of endocrinal disorders, chronic hepatic diseases, maintenance on renal replacement therapy, fulminant infections or refusal of participation in the study were the study exclusion.

Evaluation tools

1. Determination of demographic data including age, gender and body mass index (BMI) and the presence of associated comorbidities.
2. History taking from patients or their akin, concerning the presence of any exclusion criterion and for the cause of admission to ICU.

3. Acute physiology and chronic health evaluation II (APACHE II) score which is the sum of acute physiology score that consisted of 12 items (Appendix I), for a score range of 0-71 with the increasing score associated with a higher mortality rate (MR) **(Wagner and Draper 1984)**.
4. Injury severity score (ISS), which is an anatomical scoring system for patients with multiple injuries where the highest abbreviated injury scale (AIS) in each body region is used (appendix II) and ISS is calculated as the sum of the scores of the three most severely injured body regions and ranges between 0 and 75 with ISS of 75 points to an un-survivable injury **(Baker et al., 1974)**.
5. Sepsis-Related Organ Failure Assessment (SOFA) for the assessment of the status of patients admitted with sepsis/septic shock (appendix III) **(Vincent et al., 1996)**. Septic shock was defined as severe sepsis with sepsis-induced hypotension persisting despite adequate fluid resuscitation and requiring the administration of vasopressors **(Levy 2003)**.
6. At-admission serum levels of thyroid hormones; fT4, fT3, and rT3, in addition to estimation of serum TSH were estimated at the hospital clinical pathology lab.
7. Evaluation of thyroid function status according to the estimated hormonal profile and the calculated fT3/fT4 ratio as follows:
   - Patients who had a ratio ranging between 2 and 2.2 with normal serum TSH were considered euthyroid patients **(Sesmilo et al., 2011)**. Normal thyroid was confirmed by bedside US thyroid scan.
   - Patients who had a ratio higher than 2.2 with low serum TSH were considered to have hyperthyroidism **(Baral et al., 2017)**.
   - Patients who had a ratio <2 with normal or low serum TSH were diagnosed as NTIS and were categorized as NTIS-low T3/normal T4 (Type-I NTIS) if serum T4 levels were about normal levels and as NTIS-low T3&T4 (Type-II NTIS) if serum T4 levels were low and thyroid scan was normal **(Nomura et al., 2017)**.

Follow-up: Patients were observed for development of In-ICU complications; acute kidney injury (AKI), progress of sepsis to septic shock, and acute cardiac or cerebrovascular insults. Also, the ICU length of stay and In-ICU MR were registered.

Grouping: Patients were categorized according to survival outcomes at the time of ICU discharge into two groups: the survivors' group (SG), which included patients who were discharged alive from ICU, irrespective of their outcomes during later ward stay, and the non-survivors' group (NSG) who had died during their ICU stay and this group included all-cause death.

Outcomes

1. The relation between thyroid hormonal levels and follow-up outcomes.
2. The ability of estimated thyroid hormones and the fT3/fT4 ratio for the prediction of outcomes.

Statistical analysis

The Kolmogorov-Smimov test of normality and the normal Q-Q plots were used to test the data normality. The significance of the difference between patients' groups according to survival was determined by the ANOVA test Plus Tukey HSD for analysis of variance and the Chi-square test for analysis of frequencies using

IBM-SPSS software (Ver. 22, 2017; IBM, USA). Relations between studied variates were evaluated by Pearson's correlation analysis. The Receiver Operating Characteristic (ROC) curve was used to evaluate the ability of clinical and lab variates to predict outcomes according to the significance of the area under the ROC curve (AUC) and its significance versus the area under the reference line. Regression analysis was used to verify the clinical and lab variate for prediction of outcome that included the complication and mortality rates encountered during patients' ICU stay. P-value indicates significance if less than 0.5.

Results

The evaluation process detected 232 patients admitted to ICU fulfilling the inclusion criteria, while 33 patients were excluded. During ICU stay, 67 patients died with an all-cause mortality rate of 28.9% (**Fig.1**).

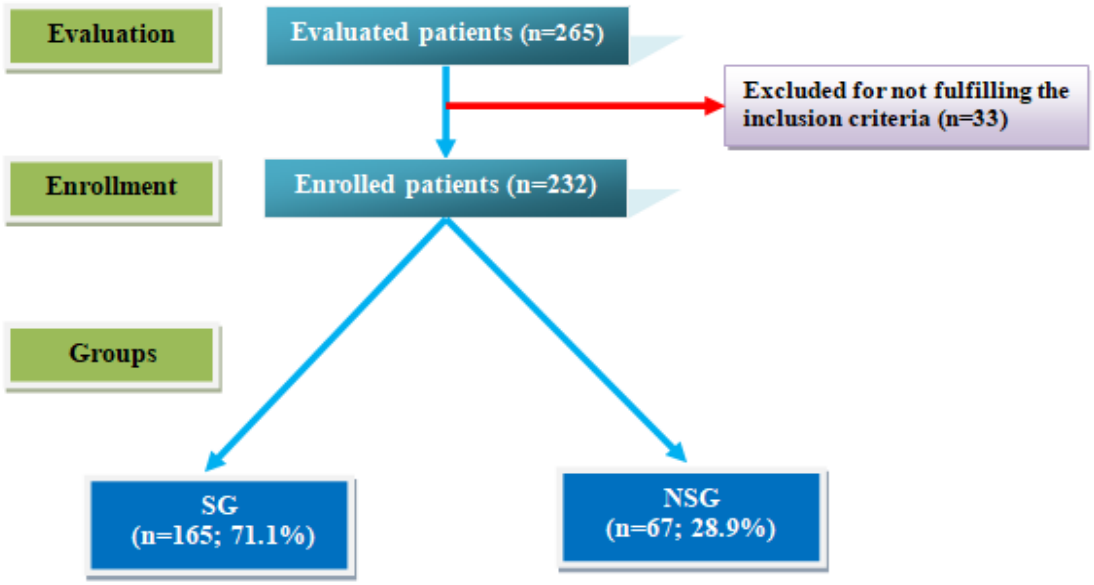

Fig. 1. Study flowchart

Patients' characteristics in survivors and non-survivors groups are shown in (**Table.1**). Patients of NSG were significantly older and obese and were mostly males. A high percentage (49.6%) of patients was admitted for immediate postoperative care with non-significant differences between both groups as regards the type of surgery. The frequency of trauma and sepsis patients was significantly higher among patients of NSG than SG. The mean value of the APACHE II score of total patients of NSG was significantly higher than patients of SG. Further, mean values of SOFA score of sepsis patients and ISS score of trauma patients were significantly higher in NSG than SG.

Table 1.Patients' characteristics in survivors and non-survivors groups

Data		SG (n=165)	NSG (n=67)	P
Age (years)*		40±5.7	42.3±5.4	0.0034
Gender†	**Male**	68 (41.2%)	41 (61.2%)	0.006*
	Female	97 (58.8%)	26 (38.8%)	
Body mass index (kg/m^2)†	**Average**	29.5±3.1	30.8±2.7	0.0014
	Overweight	88 (53.3%)	19 (28.4%)	0.0054

		Obese	77 (46.7%)	48 (71.6%)	
Professional Diagnosis†	**Postoperative**	**Neurosurgery**	22 (13.3%)	3 (4.5%)	0.471
		Cardiac surgery	25 (15.2%)	8 (11.9%)	
		Chest surgery	17 (10.3%)	6 (9%)	
		Abdominal surgery	29 (17.6%)	5 (7.5%)	
		Total	93 (56.4%)	22 (32.8%)	0.0048
	Trauma		25 (15.1%)	17 (25.4%)	
	Sepsis		47 (28.5%)	28 (41.8%)	
APACHE II score (N=75)*			8.4±2.3	13±2.9	<0.001
SOFA score for sepsis patients (N=75)*			5.6±1.4	7±1.6	0.0001
AIS score for trauma patients (N=42)	**Description of injury severity†**	**Minor**	9 (36%)	0	0.0006
		Moderate	8 (32%)	2 (11.8%)	
		Serious	7 (28%)	5 (29.4%)	
		Severe	1 (4%)	7 (41.2%)	
		Critical	0	3 (17.6%)	
	ISS*	**Average**	16.6±13.5	32.5±16.2	0.0014

One-way ANOVA test Plus Tukey HSD * and Chi-square test †;SG = survivors' group; NSG = non-survivors' group. APACHE II= The Acute Physiology and Chronic Health Evaluation Classification System II. SOFA= Sepsis-Related Organ Failure Assessment. AIS= Abbreviated Injury Scale,. .

The mean duration of ICU stay was longer for patients of NSG in comparison to patients of SG. During ICU stay, 125 patients developed complications for In-ICU CR of 53.9%, CR was significantly higher (P<0.001) among NSG patients (**Fig. 2**).

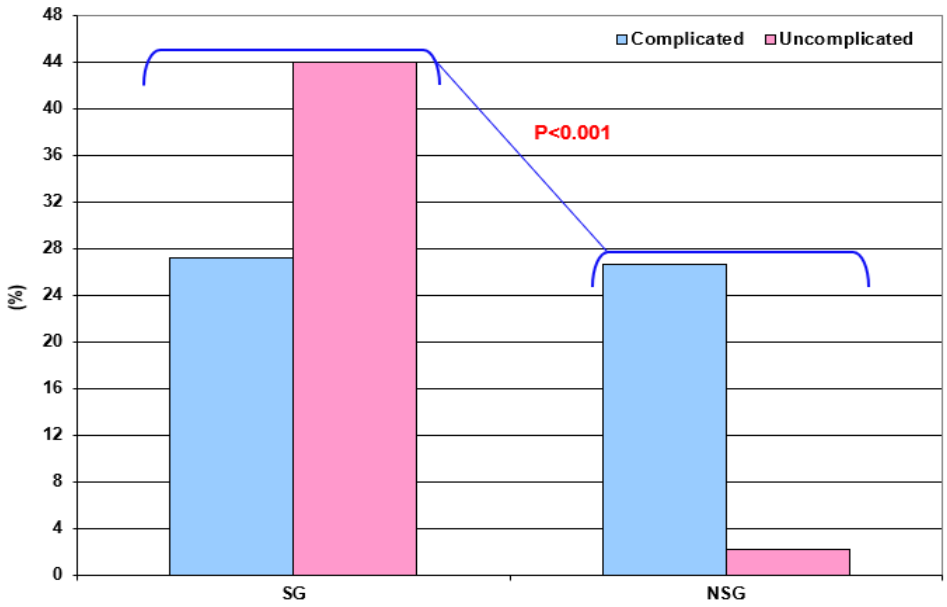

Fig.2. The incidences of complications in the survivors and non-survivors' groups.

The most commonly encountered complications are acute kidney injury and acute cardiac and cerebrovascular accidents with significantly (P=0.025) higher frequency among non-survivors (**Table.2**).

Table 2. Duration of ICU stay, the overall incidence and types of the various complications in the whole admitted cases and in survivors and non-survivors' groups

Findings		Total enrolled patients (N=232)	SG (N=165)	NSG (N=67)	P
Duration of ICU stay (h)*		126.3±80	119.7±69.2	141.1±102.2	0.014
The overall incidence of complications†	**Complicated**	125 (53.9%)	63 (38.2%)	62 (92.5%)	<0.001
	Uncomplicated	107 (46.1%)	102 (61.8%)	5 (7.5%)	
	Total	232 (100%)	165 (100%)	67 (100%)	
The incidences of the various types of complications†	**Acute kidney injury**	61 (48.8%)	38 (60.3%)	23 (37.1%)	0.025
	Acute cardiac insult	33 (26.4%)	14 (22.2%)	19 (30.6%)	
	Cerebrovascular accident	21 (16.8%)	10 (15.9%)	11 (17.7%)	
	Uncontrolled bleeding	6 (4.6%)	1 (1.6%)	5 (8.1%)	
	Coma	4 (3.2%)	0	4 (6.5%)	
	Total	125 (100%)	63 (100%)	62 (100%)	

One-way ANOVA test Plus Tukey HSD * and Chi-square test †. SG = survivors group. NSG = non-survivors group.

The mean levels of serum TSH and fT4 were non-significantly lower in the at-admission samples of NSG than in SG patients. On the contrary, the mean value of serum fT3 was significantly lower (P=0.0062) with significantly higher serum rT3 levels in samples of patients of NSG thus indicating disturbed thyroid function in direction of NTIS (**Table.3, Fig. 3**). The mean value of the calculated fT3/fT4 ratio was significantly (P=0.0044) lower in samples of non-survivors than survivors thus indicating the NTIS (**Table 3, Fig. 4**).

According to the fT3/fT4 ratio, 102 patients (44%) had a ratio of <2 (NTIS), 100 patients (43.1%) had fT3/fT4 ratio of 2-2.2 (Euthyroid state), and 30 patients (12.9%) had a ratio of >2.2 (hyperthyroidism)with significant (P=0.0013) differences between both groups. The frequency of patients who had fT3/fT4 ratio of <2 was significantly lower, while the frequency of patients who had fT3/fT4 ratio of 2-2.2 was significantly (P=0.0005) higher among survivors (**Table 3, Fig. 5**).

Table 3. At-admission, thyroid hormonal profile of survived and non-survived groups.

Variate	SG (n=165)	NSG (n=67)	P-value
Serum TSH (mIU/L)*	2.15±1.1	1.98±1	0.263
Serum fT4 (ng/dl)*	1.46±0.35	1.38±0.34	0.104
Serum fT3 (pg/ml)*	267.55±119.9	221.87±98.6	0.0062
Serum rT3 (ng/dl)*	18.55±9.14	22.1±10.6	0.0117

fT3/fT4 ratio	**Mean (±SD)***		1.82±0.55	1.6±0.48	0.0044
	Frequency †	**NTIS (ratio<2)**	61 (37%)	41 (61.2%)	0.0007
		Euthyroid (ratio=2-2.2)	83 (50.3%)	17 (25.3)	0.0005
		Hyperthyroid (ratio>2.2)	21 (12.7%)	9 (13.4%)	0.885

One-way ANOVA test Plus Tukey HSD * and Chi-square test †;-SG = survivors' group. NSG = non-survivors group.

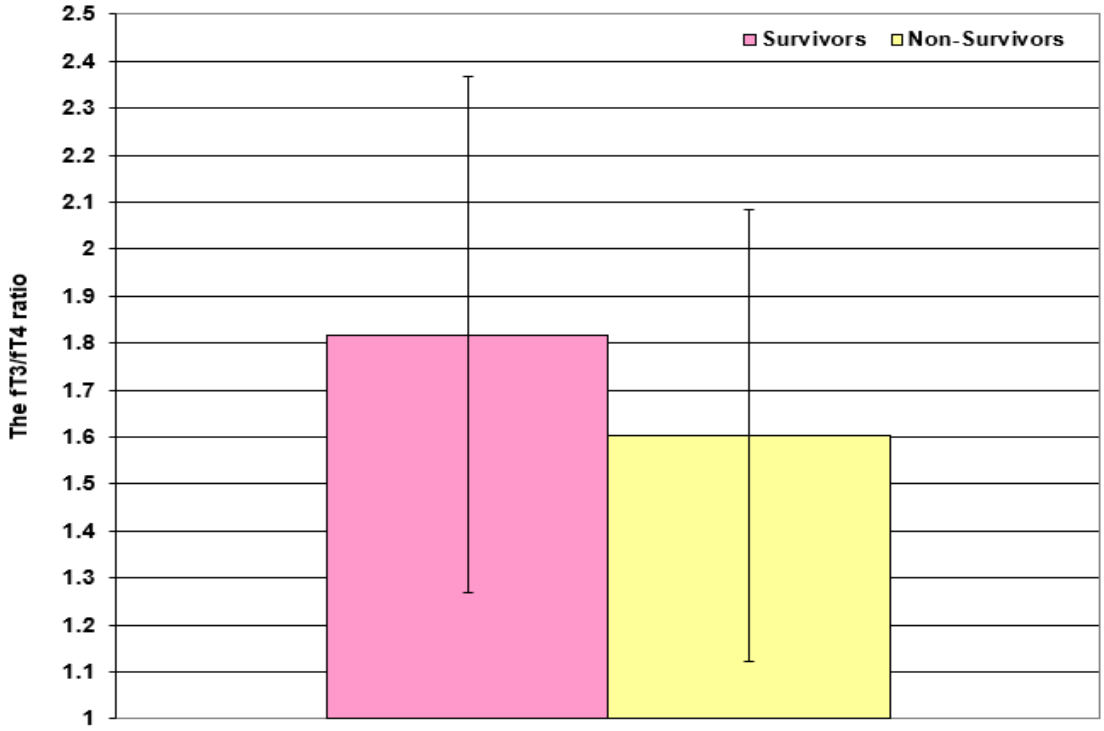

Fig.3. Serum levels of fT3 and fT4 at time of admission to surgical intensive care in survivors and non-survivors groups.

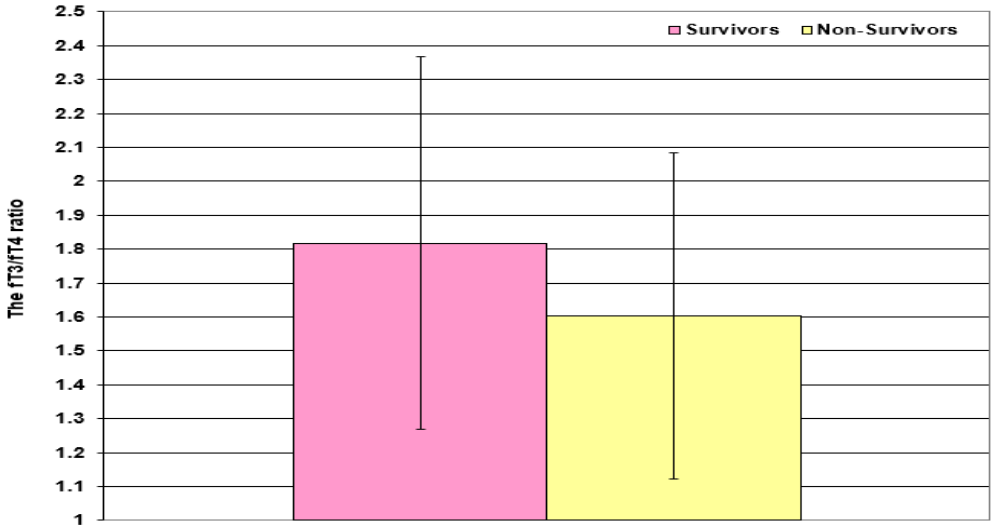

Fig.4. The calculate fT3/fT4 ratio at time of admission to surgical intensive care in survivors and non-survivors groups

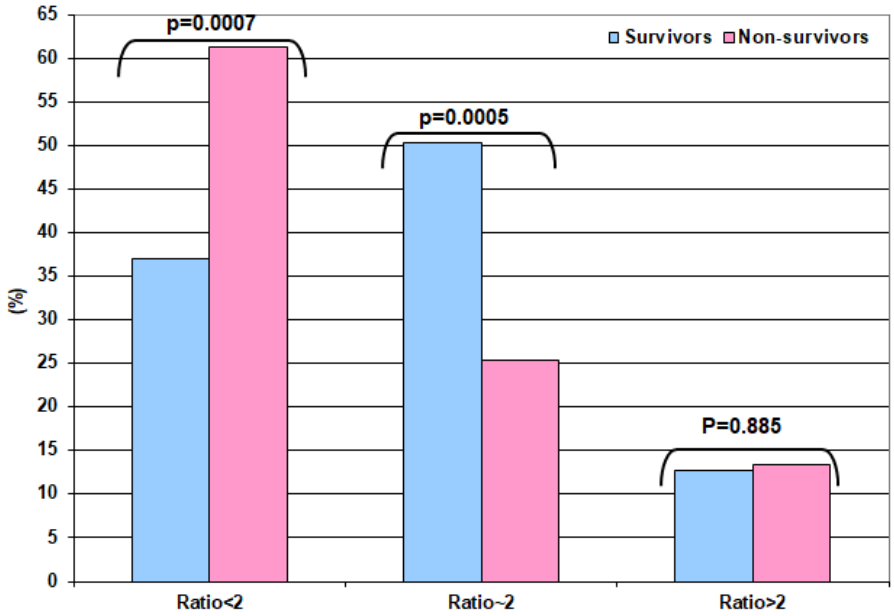

Fig.5. Patients distribution according to the values of the calculated fT3/fT4 ratio in survivors and non-survivors groups.

Patients had NTIS with fT3/fT4 ratio of <2 were of either Type-I NTIS (n=97) or Type-II NTIS (n=5) according to estimated serum levels of fT4 and findings on bedside US imaging. Among patients who had fT3/fT4 ratio of 2-2.2 (Euthyroid state); 9 patients had low serum T3 and T4 levels and bedside US imaging of these nine patients excluded glandular pathology and were considered as Non-NTIS cases. Furthermore, patients who showed a ratio of >2.2 (Hyperthyroidism) had near normal serum fT4 with increased serum levels of fT3 giving rise to the high ratio, but bedside US imaging of thyroid gland excluded any thyroid pathology.

The reported In-ICU, CR, and MR showed variant correlations with patients' demographic and clinical data and with the results of the evaluation of thyroid function tests as shown in (**Table.4**).

Table 4. Correlation between clinical and Lab data and patients' outcomes

Variates		Complications		Mortality	
		r	P	r	P
Clinical data	**Age**	0.130	0.048	0.179	0.006
	Male gender	0.101	0.126	0.004	0.956
	BMI	0.172	0.009	0.182	0.005
	APACHE II score	0.412	<0.001	0.646	<0.001
	ICU stay	0.066	0.314	0.120	0.067
Serum level of	**TSH**	0.059	0.730	0.074	0.263
	fT4	-0.042	0.520	0.107	0.104
	fT3	-0.151	0.021	0.179	0.006
	rT3	0.009	0.887	0.165	0.012
	T3/T4 ratio	-0.205	0.002	0.204	0.002

The ROC curve analysis of demographic and clinical data of the studied patients defined obesity and high at-admission APACHE II score as the positive significant predictors for the development of In-ICU

complications (**Fig.6a**) Regarding the predictors for mortality, the ROC curve analysis defined high at-admission APACHE II score and development of In-ICU complications as the highly significant positive predictors for patients' mortality **(Fig. 6b, Table.5**).

Table 5. The Receiver Operating Characteristic curve analyses of patients' clinical data as identifiers for patients vulnerable to developing complications and differentiate the non-survivors

Dependent variates	Independent variates	AUC	SE	P	95%CI
Development of complication	**Age**	0.566	0.038	0.083	0.492-0.640
	Male	0.550	0.038	0.186	0.476-0.625
	BMI	0.607	0.037	0.005	0.534-0.680
	APACHE II	0.742	0.032	<0.001	0.679-0.805
	ICU stay	0.514	0.038	0.712	0.440-0.588
Survival	**Age**	0.385	0.041	0.006	0.305-0.465
	Male	0.502	0.042	0.962	0.420-0.584
	BMI	0.388	0.039	0.007	0.310-0.465
	APACHE II	0.116	0.025	<0.001	0.066-0.166
	Complication	0.228	0.031	<0.001	0.167-0.290
	ICU stay	0.465	0.046	0.406	0.375-0.555

AUC: Area under the curve; SE: Standard error; CI: confidence interval; P value indicates the significance of difference of variate's AUC in comparison to area under the reference line

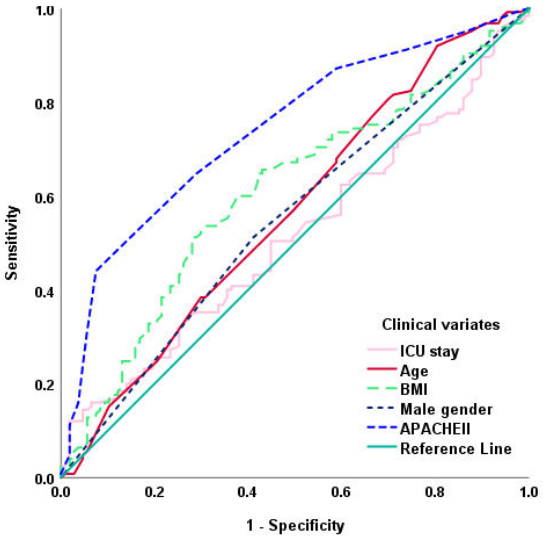

Fig. 6a: ROC curve analysis of clinical variates as predictors for In-ICU complications.

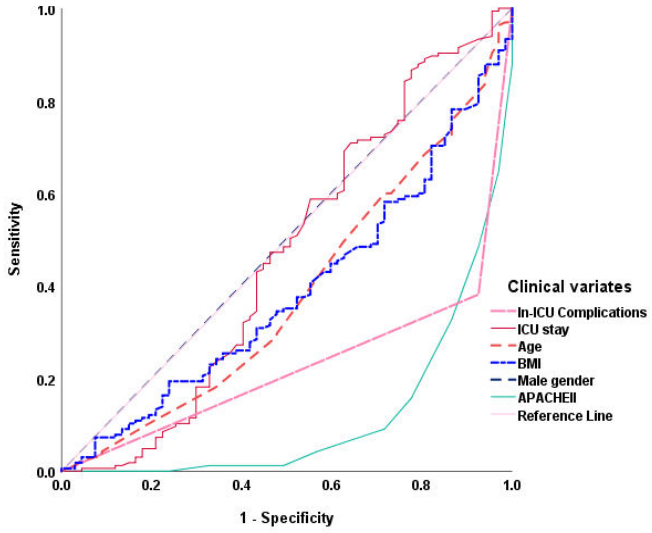

Fig. 6b: ROC curve analysis of clinical variates as predictors for survival.

The ROC curve analysis showed that the AUCs for levels of at-admission fT3 and fT3/fT4 ratio were significant in comparison to the area under the reference line and so could be applied as early predictors for oncoming complications **(Table. 6, Fig. 7a**). Regarding mortality, decreased levels of all thyroid hormones could deleteriously affect the survival of ICU patients and ROC curve analysis defined these decreased levels as predictors for the oncoming mortality (**Table.6, Fig. 7b**).

Table 6. The ROC curve analysis of at-admission lab findings for early prediction of the development of complications and the possibility of mortality

Dependent variates	Independent variates	AUC	SE	P	95%CI
Development of complication	TSH	0.535	0.038	0.363	0.460-0.609
	fT4	0.458	0.039	0.266	0.382-0.533
	fT3	0.423	0.039	0.042	0.348-0.497
	rT3	0.508	0.038	0.833	0.433-0.583
	T3/T4 ratio	0.388	0.037	0.003	0.315-0.461
Survival	TSH	0.533	0.041	0.435	0.452-0.614
	fT4	0.593	0.041	0.026	0.513-0.673
	fT3	0.619	0.040	0.005	0.541-0.697
	rT3	0.392	0.042	0.010	0.310-0.474
	T3/T4 ratio	0.608	0.041	0.010	0.527-0.689

AUC: Area under the curve; SE: Standard error; CI: confidence interval; P value indicates the significance of difference of variate's AUC in comparison to area under the reference line

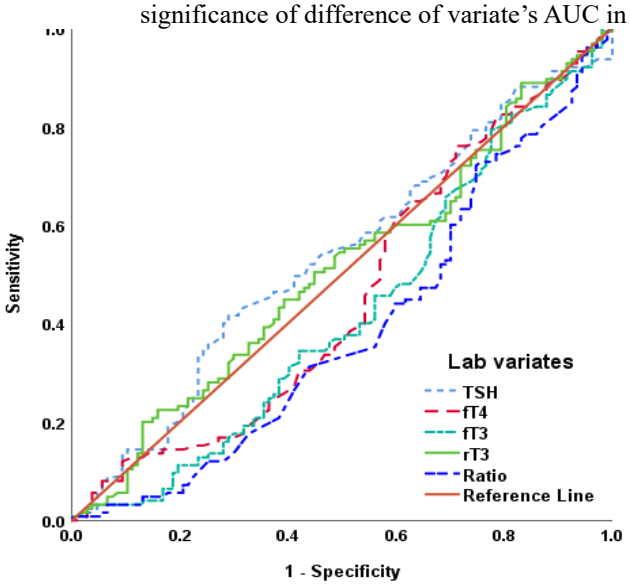

Fig. 7a: ROC curve analysis of thyroid hormones estimated in samples obtained at ICU admission to predict the oncoming In-ICU complications

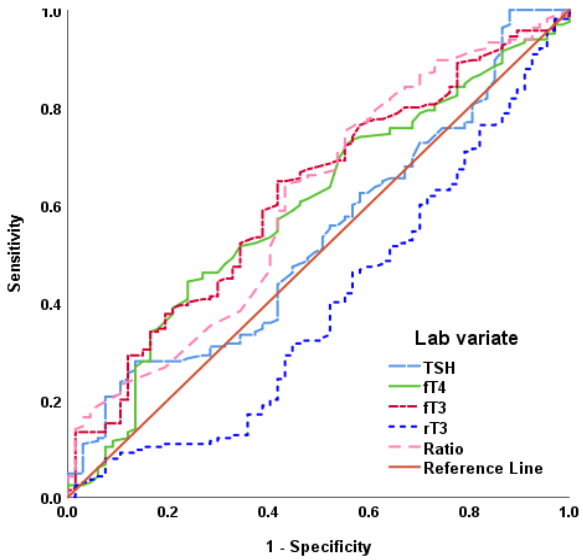

Fig. 7b: ROC curve analysis of thyroid hormones estimated in samples obtained at ICU admission as early predictors for ICU complications

The Multivariate Regression analysis assured the predictability of a high APACHE II score for the oncoming In-ICU complications (β=0.412, P<0.001). Concerning the serum hormonal levels, Multivariate Regression analysis defined low fT3/fT4 ratio as a positive significant predictor for oncoming complications and mortality (β=0.205; P=0.002).

Discussion

The current study detected disturbed thyroid hormonal homeostasis in all patients admitted to the surgical ICU as evidenced by low levels of fT3, the most potent thyroid hormone, and increased levels of rT3, the inactivated thyroxin. Moreover, this turmoil in the thyroid hormonal milieu was more evident in patients who developed In-ICU complications, especially the non-survivors. Correlation analysis showed a positive relation between survival and serum fT3, while In-ICU complication rate (In ICU CR) and ICU stay duration were inversely related to serum fT3, but directly related to at-admission

APACHE II score. Furthermore, ROC curve and regression analyses illustrated these results and defined high at-admission APACHE II score, low fT3, and high rT3 as positive predictors for high In-ICU CR and as negative predictors for survival. Similarly, **Praveen et al., 2023** reported significantly lower T3 in non-survivors and a negative relation between serum T3 and readmissions and ICU stay, while such relations were positive for APACHE II score and both could predict mortality as judged by AUC.

Interestingly, the calculated fT3/fT4 in at-admission samples did better than just the estimation of serum thyroid hormone levels for distinguishing ICU patients vulnerable to developing IN-ICU complications or mortality as judged by statistical analyses. In support of the prognostic ability of the fT3/fT4 ratio for oncoming complications or mortality of critically ill patients, **He et al., 2022** reported that the ROC curve indicated a good predictive value of the fT3/fT4 ratio for major adverse cardiac events and was an independent risk factor for these events after acute myocardial infarction. In addition to its prognostic value, **Lacámara et al., 2020** found the diagnosis of resistance to external thyroxin therapy is confirmed by decreased T3/T4 and T3/rT3 ratios, and elevated rT3/T4 ratio. Thereafter, **Liu et al., 2022** showed that the fT3/fT4 ratio significantly affected the prevalence of non-alcoholic fatty liver disease and found visceral adiposity index partly mediated the indirect effect of the fT3/fT4 ratio on such prevalence and concluded that fT3/fT4 ratio and visceral adiposity index were predictors of fatty liver disease.

Furthermore, the current study defined the ability of the fT3/fT4 ratio at a level of <2 as previously documented by **Nomura et al., 2017** to act as a complementary diagnostic tool to bedside ultrasonography for identifying patients who had disturbed thyroid hormonal milieu and statistical analyses showed the high predictability of the fT3/fT4 ratio of <2 for mortality than just the estimation of serum thyroid hormones. Similarly, **Praveen et al., 2023** documented the high frequency of NTIS among critically ill patients and the ability of the fT3/fT4 ratio to significantly predict mortality. Also, Among critically ill pediatric patients, **Sahu et al., 2022** detected both Type I and II NTIS with a higher frequency of Type I and found non-survivors had significantly lower admission levels of both fT3 and fT4. Further, **Carreras et al., 2023** documented that in critically ill children, the presence of NTIS is a good predictor of a high mortality risk that was aggravated if there are low fT4 levels.

The detected relation between thyroid dysfunction and the severity of In-ICU complications and mortality indicated the necessity for evaluation of thyroid hormonal levels that could be used as an additional low-cost marker of mortality.

The study limitations included being a single center study, estimation of blood levels of sepsis markers to evaluate its impact and relation to the disturbed thyroid functions.

Conclusion

Disturbed thyroid hormonal homeostasis is a neglected issue that seriously affects the outcomes of critically ill patients admitted to surgical ICU. Low at-admission serum levels of fT3, low fT3/fT4 ratio, and high rT3 levels could predict the vulnerability for getting In-ICU complications and mortality. The fT3/fT4 ratio of <2 could differentiate patients who had NTIS which showed high incidence and relation to worse outcomes.

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