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Original Research Article

A study to evaluate serum free triiodothyronine levels as a predictive indicator of outcome in critically ill children

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ABSTRACT

Background: Critical illness is a life-threatening multisystem process requiring support of failing vital organ systems without which survival would not be possible. Euthyroid sick syndrome is one of the commonly seen endocrine changes in critically ill patients and is considered to be associated with adverse outcome in ICU patients. Objective of this study was to assess free triiodothyronine (FT3) in critically ill children and to associate it to the disease severity and clinical outcome in comparison to PRISM score.
Methods: This was an observational study conducted on 120 critically ill children aged between 1month and 18 years admitted in PICU of a tertiary care hospital. All children who met inclusion and exclusion criteria were subjected to initial evaluation, PRISM III scoring and also FT3 levels was estimated twice in the critically ill patients.
Results: In present study, out of 120 subjects studied, 34 succumbed and 86 survived. Low FT3 was seen in 90 (75.00%) children. The mean level of FT3 was significantly lower at admission and discharge in non-survivors than in survivors ($P<0.01$) and also Compared with survivors, non-survivors had higher PRISM III scores (26.65±9.64vs 15.21±7.38, $P<0.001$). In survivors there was a significant improvement in the mean levels FT3 from admission to discharge ($P<0.01$) Where as in non-survivors there was a further decrease in the mean levels of FT3 however it was not statistically significant ($P>0.05$). Serum FT3 at discharge is a good predictor of mortality with AUC of 0.9175±0.0620.
Conclusions: FT3 is good independent predictor of ICU mortality.

Keywords: Critically ill children, Euthyroid sick syndrome, Free triiodothyronine

INTRODUCTION

Critical illness is a life-threatening multisystem process requiring support of failing vital organ systems without which survival would not be possible and also can result in significant morbidity or mortality.[1] This condition can be evoked by a variety of insults such as severe medical illnesses, multiple trauma and complicated surgery. Critical illness is thus the ultimate form of severe physical stress, and all the immediate biological responses that are evoked are expected to be of greater magnitude in critically ill patients.

The effects of critical illness are manifold and not the least among them is the profound changes seen in endocrine and metabolic systems. These immediate stress responses comprise many endocrine adaptations that are presumably directed toward providing the required energy for the fight-or-flight response in a background of exogenous substrate deprivation.[1]

Among such changes Euthyroid sick syndrome (ESS) is one of the commonly seen endocrinological changes in critically ill patients. The incidence of non-thyroid illness syndrome is 11-18% in non-selected hospitalised patients

and increases up to 65-70% in ICU.[2] Euthyroid sick syndrome is described as abnormalities in circulating thyroid hormone levels without pre-existing hypothalamic-pituitary or thyroid gland dysfunction in the setting of a non-thyroidal Illness. It reverts back to normal after recovery from the non-thyroidal Illness.[1]

In the acute phase of critical illness, the alterations in thyroid hormones present as decreased T3 and increased T4 and rT3, as well as normal TSH. In the chronic phase of critical illness, central hypothyroidism develops, and NTIS presents as decreased T3, decreased T4 and decreased TSH. In the recovery phase of critical illness, the thyroidal axis begins with a rise in serum TSH, which is eventually followed by normalization in T4 concentration.[2]

Among patients in different phases of critical illness, it was seen that levels of T4, FT4 and TSH were increased, decreased or normal, but the T3 or FT3 level was generally reduced in patients with NTIS. Therefore, TT3 or FT3 level may be better than TSH and T4 level (or FT4 level) for predicting ICU outcomes.

The TT3 or TT4 level can be affected by the concentration of thyroxine-binding globulin (TBG) or the binding ability of TBG, which may be affected by some health conditions, such as liver disease, and by a lot of commonly used drugs, including glucocorticoids, nonsteroidal anti-inflammatory drugs, furosemide and heparin. Conversely, FT3 and FT4 levels are not affected by these factors. Thus, FT3 and FT4 levels may be better than TT3 and TT4 levels for predicting ICU outcomes.

Many studies have confirmed the association between non-thyroidal illness and adverse outcome. Although in adults the endocrine and metabolic changes during the acute phase of critical illness have been viewed as adaptive it is still unclear to which extent some of these defence mechanisms may hypo- or hyper-respond and as a consequence be harmful.[1]

The course of critical illness in children differs from adults. Critical illness in children may develop quickly and if children survive the impact of acute critical illness, it is rapidly followed by recovery. Unlike adults, chronic or protracted critical illness is fairly uncommon in children.

Understanding of the endocrine and metabolic changes of paediatric critical illness, especially those in the acute phase, is important and may improve outcome, as it allows the rational use of pharmaceutical interventions. It may also reveal endocrine and metabolic changes to be used as prognostic markers.

This prompted us to study: Serum thyroid hormone levels as a predictive indicator of outcome in critically ill children.

METHODS

This was an observational study conducted on 120 critically ill children aged 1month to 18 years admitted to PICU of tertiary care, teaching hospital, Bangalore, Karnataka over a study period of 12 months. Ethics approval for the study was obtained from the Institutional Review Board.

All critically ill children admitted to PICU in the age group of 1 month to 18 years were included in the study.

Inclusion criteria:

1 month to 18 year critically ill children admitted to KIMS PICU.

Exclusion criteria:

- Known case of thyroid disorder or patients with clinical evidence of thyroid dysfunction.
- Family history of thyroid illness.
- Patients who are on drugs interfering with the thyroid hormone function.

Detailed history and examination were done in all the patients including the relevant investigation and the data were collected at admission.

Method of collection of data

Informed and written consent will be taken from the parent/ guardian of the child. Detailed history was taken followed by thorough general physical examination and systemic examination. The following investigations were done in all samples complete hemogram, ABG, Serum electrolytes, GRBS, RFT, PT and APTT.

Free T3 level was estimated twice in the critically ill patients.

- Sample 1: Admission to PICU.
- Sample 2: Discharge from PICU or if the patient condition worsens.

FT3, FT4 and TSH levels were measured using the chemiluminescent immunoassay system. The normal ranges of serum hormone FT3- 2.6 to 4.4pg/ml. PRISM 3 score was used to predict mortality.

Statistical analysis

The Statistical software namely SPSS 18.0, and R environment ver.3.2.2 were used for the analysis of the data and Microsoft word and Excel have been used to generate graphs, tables etc. Statistical analysis was done using the Chi square significance test, student t-test, correlations and binary logistic regression. All statistical analysis was considered significant if p value<0.05.

RESULTS

In present study 142 children who met with inclusion criteria were enrolled in to the study. Out of which 120 children were included in the study and remaining 22 children in whom the second sample could not be obtained due to unavoidable consequences were excluded.

Statistical analysis was done for remaining 120 children and results are presented as follows. In present study, out of 120 subjects studied, 34 succumbed and 86 survived.

Table 1: Mean age of the study participants (N=120).

	Mean	SD	Median	Inter quartile range	P value*
Survivor (n=86)	4.7	4.83	2	1.2-7	
Non-survivor (n=38)	5.05	5.26	3	0.66-12	0.99
All participants	4.8	4.91	2.5	1.05-7	

Mean age of the study population was 4.8 years. No significant association of age with mortality was seen. (P=0.99), majority belonged to age group less than 3yrs (50%). In present study, males were predominant constituting 65% (78) and females were 35% (42) with male to female ratio of 1:0.54. In present study, majority of study population stayed in hospital for 6-12 days (51.7%), followed by less than 6 days (46.7%) and only 1(1.7%) patient stayed for more than 12 days.

Table 2: System wise diagnosis with outcome (n=60).

	Non-survivor		Survivor		Total	
	N	%	N	%	N	%
Infectious disease	14	82.4	18	41.9	32	53.3
CNS	1	5.9	9	20.9	10	16.7
Respiratory system	0	0.0	9	20.9	9	15.0
Poisoning	1	5.9	3	7.0	4	6.7
Haematology	0	0.0	3	7.0	3	5.0
Miscellaneous	1	5.9	1	2.3	2	3.3
Total	17	(100.0	43	100.0	60	

Table 3: Comparison of FT3 at admission and discharge based on outcome of the study participants.

	Non-survivors	Survivors	P value*
	Mean (SD)	Mean(SD)	
At admission	1.24 (0.63)	2.34 (1.08)	0.0002
At discharge	1.17 (0.96)	3.05 (0.94)	<0.001*
P value	0.29	<0.001	

Table 4: Correlation of FT3 with PRISM score.

	r	P value
At admission	-0.3338	0.009
At discharge	-0.2878	0.045

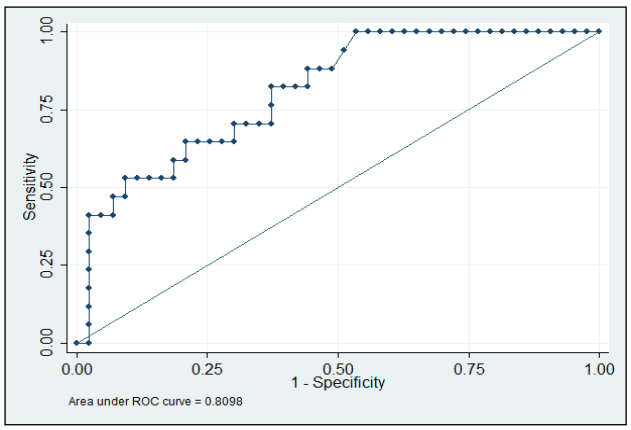
In present study, it is seen that there is moderate negative correlation between FT3 and PRISM score; however, it was not statistically significant.

Table 5: Binary logistic regression between outcome (Death) as dependent variable and prism score and FT3 at admission as independent (predictor).

	Unadjusted odds ratio (95% CI)	Adjusted odds ratio (95% CI)	P value
PRISM score	1.153 (1.066-1.247)	1.120 (1.015-1.236)	0.024
FT3 at admission	0.187 (0.067-0.525)	0.412 (0.112-1.512)	0.181

In present study, it is seen that as the PRISM score increases there was a significant increased risk of mortality with odds ratio 1.12, (P value 0.024).

Also, for every increase in values of FT3 there was a reduced risk of mortality with odds ratio 0.412 however it was not statistically significant (P value- 0.181, 0.208 and 0.236 respectively).



ROC: Receiver Operator Characteristic

Figure 1: ROC curve for free T3 at admission to give the cut off values for prediction of death.

It is seen that sensitivity FT3 is good in predicting outcome (death) however specificity is poor. No cut-off value for FT3 could be demonstrated and correlate the magnitude of FT3 levels with patient's outcome. In present study as seen in the above ROC curve it was seen that FT3 levels at discharge is a powerful predictor of outcome (death) and at the level of FT3- 1.98pg/ml, sensitivity was 90.91% and specificity was 84.21% in predicting outcome.

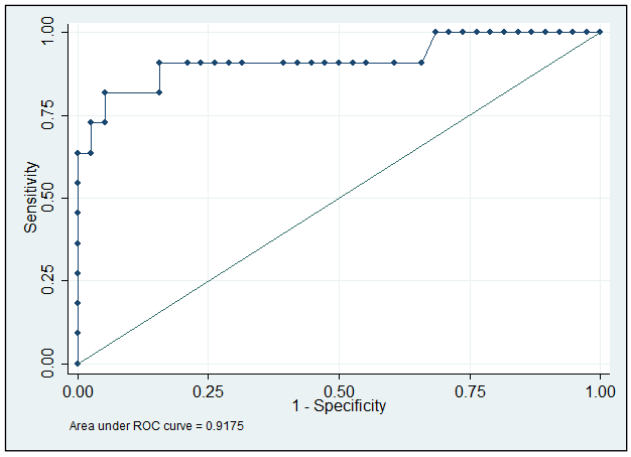


Figure 2: ROC curve for FT3 at discharge to give the cut off values for prediction of death.

DISCUSSION

On the basis of the normal ranges mentioned above, the commonest change seen was low serum FT3 level, 75.00% (45) similar to other studies.[3-5] This finding has not been reflected uniformly in other studies. Some studies failed to demonstrate significant lower serum FT3 in critically ill patients.[6]

The mean PRISM III score was 18.45±9.54 points. The primary reasons for PICU admission were infectious disease 53.3% (32), followed by pulmonary and nervous system ailments. Among infectious disease, dengue (40%) is the leading cause due to seasonal epidemic in our region. Whereas in other studies pulmonary and cardiovascular disease was seen to more common.[5,6]

Table 6: Performance of variables in predicting mortality.

Variable	AUC ROC	P value	Cut off value	Sensitivity (%)	Specificity (%)
FT3 at admission	0.8098±0.0583	<0.001	≤1.87	82.35	68.33
FT3 at discharge	0.9175±0.0620	<0.001	≤1.98	90.91	84.21

A total of 17 patients (28.33%) died during their PICU stay. The mean levels of FT3 was significantly lower at admission in non-survivors than in survivors (all P <0.01) and also Compared with survivors, non-survivors had higher PRISM III scores (26.65±9.64vs 15.21±7.38, P <0.001). It was also seen that the mean levels of FT3 was significantly lower even at discharge in non-survivors than in survivors (all P <0.01) and also compared with survivors.

It was also noted in survivors that there was a significant improvement in the mean levels FT3 from admission to discharge (P <0.01) similar to other studies.[7] However in non-survivors there was a further decrease in the mean levels of FT3 but it was not statistically significant (P>0.05) whereas in other studies Wang et al and Suvarna J, Fande C, studies showed significant decrease in the mean values of thyroid profile.[7,8] This probably because in present study majority expired within 24-48 hours of admission and the second sample was drawn within this short interval, hence a significant difference between the two samples has not been observed.

In present study it was observed that the serum FT3 levels at admission as the good baseline discriminator between survivors and non-survivors, which can prognosticate the clinical status of the critically ill patients. Whereas wang et al similar observation, Anand et al failed to demonstrate the same in the infants.[5,7] Why the results of the previous studies are different from those of present study can be attributed to the different populations included in the other studies.

It was also noted that serum FT3 level improved on discharge from the PICU and did not improve in those who expired. This implies that serum FT3 level closely follows the clinical status of the patients and persistently low serum FT3 level may reflect poor outcome. In this study, we found that FT3 is good predictor of ICU likewise in Wang et al study.[7]

The addition of FT3 levels to PRISM III scores could significantly improve the ability to predict ICU mortality, as demonstrated. The pathophysiological mechanism underlying the association of lower FT3, FT4 levels with worse outcomes in PICU patients has yet to be fully defined. It is still unclear whether the alteration in thyroid hormone levels during critical illness is the adaptive physiological response to stress or the maladaptive response requiring treatment.[9]

Some studies have reported that patients with heart failure have low T3 serum concentrations, which correlates with cardiac function.[10]

In short, low FT3 levels might represent an integrative measure of multiple harmful pathological processes occurring simultaneously in patients with critical illness, such as inflammation status and cardiac dysfunction, which are associated with adverse outcomes.[11,12] This hypothesis cannot completely explain the association of FT3 levels with adverse outcomes. Future studies are needed to explore further underlying mechanisms

The improvement of FT3 levels in patients who survived and non-improvement in those who expired raises an important question, 'can FT3 supplementation in critically ill patients improve survival?' controversy remains whether NTIS should be treated or it needs to be considered as an adaptive response to illness. Further studies are required to throw light on this question.

Limitations of this study was the clear that many drugs (barbiturates, benzodiazepines, furosemide, dopamine etc) may have interfered with thyroid function; it is difficult to adjust for these potential confounders in clinical practice

The present study assessed FT3 only twice i.e. at admission and at discharge. A lookout for the trend of changes in the thyroid hormone profile in the critically ill children may give us better information

Addition of control group and larger sample size would have added further strength to prognostic value of thyroid value.

CONCLUSION

The mean FT3 levels in critically ill children are low. On recovery the FT3 normalize however worsen in case of death. At admission to the PICU FT3 was low and was further reduced in children who will subsequently die and therefore more aggressive therapy may be warranted in such children. At any given point FT3 reflects the patient's clinical status and persistent low serum FT3 levels with non-improvement would spell bad prognosis and have increased risk of mortality. To conclude, FT3 is powerful predictor of ICU mortality. Addition of FT3 levels to PRISM III scores significantly improved the ability to predict PICU mortality.

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