MED-PHOENIX: JOURNAL OF NATIONAL MEDICAL COLLEGE

ORIGINAL ARTICLE

NON-THYROIDAL ILLNESS SYNDROME: A PATTERN OF THYROID DYSFUNCTION SEEN IN INTENSIVE CARE UNIT PATIENTS OF A TERTIARY CARE CENTRE

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Date of Submission : July 1, 2022
Date of Acceptance : Aug 3, 2022
Date of Publication : Aug 19, 2022

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Citation:
Sah SK, Gupta S, Marasini S, Yadav N, Jha AC, Jha S, Shrestha B. Non-Thyroidal illness syndrome: a pattern of thyroid dysfunction seen in intensive care unit patients of a tertiary care centre. Medphoenix. 2022;7(1):51-56.

DOI: 10.3126/medphoenix.v7i1.47404

Conflict of interest: None, ***Funding:*** None

Publisher: *National Medical College Pvt. Ltd.*
MedPhoenix - Journal of National Medical College (JNMC); 2022,7(1), available at www.jnmc.com.np

ISSN:2631-1992 (Online); ISSN:2392-425X (Print)

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ABSTRACT

Introduction: *The response to the endocrine mechanism including thyroid gland hormones to critical illness is a complex phenomenon. There is a marked and distinct changes in the levels of thyroid hormones in critical illness. The magnitude of the decrease in circulating tri-iodothyronine (fT3) levels (also known as non-thyroidal illness) during the first 24 hour after the onset of acute illness reflects the severity of illness and correlates with mortality. The study aims to evaluate the thyroid function test (TFT) of critically ill patients. The results of the study will be helpful in determining the thyroid picture of the critically ill patients in our setting and definitely help in assessing the outcome of the patient admitted in ICU or ward.*

Materials and Methods: *This is a hospital based cross sectional study. A total of 150 cases with the critical illness assessed as per Acute Physiology and Chronic Health Evaluation II (APACHE II) score were enrolled in the study from 12th December 2021 to 15th June, 2022. Informed written consent and ethical approval were taken.*

Result: *The majority of the cases (52%) were of geriatric age group with the mean age of 57 years. Majority of the study participants (42%) in APACHE II were from 20–24 across all participants, and both sexes. Fifty one percent of the patients had reduced fT3 levels. There was an increase in percentage of patients with decreased fT3 levels with increasing APACHE II score, compared to normal fT3 levels at similar APACHE II score and the distribution was found to be statistically significant (p = 0.0233). Of the 68 patients expired, 52 of them had low fT3 levels whereas only 16 cases expired were with the normal fT3 level, making it a strong predictor of severity and outcome.*

Conclusion: *Decrease in the levels of fT3, a condition of non-thyroidal illness, is a crucial prognostic indicator in critically ill patients which in coordination APACHE Score II can be helpful in clinical settings to predict the severity and outcome of such patients.*

Keywords: *APACHE II Score; Free tri-iodothyronine; Non-thyroidal illness; Thyroid function test.*

INTRODUCTION

The response to the endocrine mechanism including thyroid gland hormones to critical illness is a complex phenomenon. The physiological rationale behind these changes is primarily in the body to achieve homeostasis and is, of course associated with the morbidity and mortality of patients.[1] There is a marked and distinct changes in the levels of thyroid hormones in critical illness.[2] There are studies suggesting the findings of thyroid dysfunction associated with the increased

morbidity and mortality of patients admitted to Intensive Care Unit (ICU).[3] These alterations in thyroid hormone levels have been referred by various terms such as euthyroid sick syndrome, sick euthyroid syndrome, non-thyroidal illness syndrome, and low tri-iodothyronine (T3) low thyroxine (T4) syndrome. The characteristic feature are low serum levels of free and total T3 and high levels of reverse T3 (rT3), accompanied by normal or low levels of T4 and thyroid-stimulating hormone (TSH).[4,5] It have also been reported in some studies that alterations in thyroid hormone levels during non-thyroidal illness syndrome can act as independent predictors of mortality and morbidity in critically ill patients, thus proposing the inclusion of thyroid profile in these scoring systems of critically ill patients.[3,6]

In sequel of acute illness, surgery, or other types of severe physical stress, it is seen a very rapid decline in the circulating amount of T3, however plasma concentrations of rT3 rise acutely. These changes can partly be explained by reduced levels of thyroid hormone binding protein and albumin and a reduced binding activity, whereby the hormone is freed from the binding proteins and the clearance of the hormone is increased.[7]

It can also be stated that an acute alteration in the peripheral conversion of T4, due to a decreased D1 activity and an increased D3 activity[8,9], may explain these changes. In patients who are suffering from acute illnesses or any other insults for which the onset can be correctly identified, such as surgery, a very transient rise in T4 has also been documented to coincide with the rapid fall in plasma T3.[10] However, in patients admitted to the ICU for any other reasons other than surgery, patients who are considered to be more severely ill, admission plasma T4 concentrations are normal or at times even low.[11] In addition, plasma TSH concentrations measured in a single sample can be found to be transiently elevated, as occurs during surgery[10], but most often plasma TSH concentrations are in the normal range in patients admitted to the ICU. But, by analysing TSH time series, it has become clear that in this acute phase of illness, the normal nocturnal TSH surge is absent.[12,13] The magnitude of the decrease in circulating T3 levels during the first 24 h after the onset of acute illness reflects the severity of illness and correlates with mortality.[14-17]

In this study, we want to establish the relationship between critical illness (based on the Acute Physiology and Chronic Health Evaluation II [APACHE II] score) and thyroid dysfunction. The result of the study will be helpful in determining the thyroid picture of the critically ill patients in our setting and definitely help in assessing the outcome of the patient admitted in ICU or ward.

MATERIALS AND METHODS

This is a hospital based cross sectional study carried out in the Department of Laboratory Medicine (Biochemistry) and Internal Medicine, Intensive Care Unit (ICU) of National Medical College, Birgunj, Nepal. A total of 150 cases admitted in ICU with the chronic critical illness as assessed as per Acute Physiology and Chronic Health Evaluation II (APACHE) Score and diagnosed by the internist, a co-author of this study, were enrolled in this study. Informed written consent in understandable language either Nepali or local language was obtained from the participants/attendants. Patients with a known history of thyroid disorders, intake of drugs that can alter thyroid hormone levels, and pregnant patients were excluded from the study. The samples from the cases were analyzed for the thyroid function test (TFT). In a period of six months, 150 cases of chronic illness admitted in ICU from the month of 12th December 2021 to 15th June 2022 were enrolled in the study. Ethical approval for the study was obtained from Institutional Review Committee (IRC) of National Medical College Teaching Hospital (Ref: F-NMC/562/078-079). The samples of the subjects was taken following the optimum standard protocol and Thyroid Stimulating Hormone (TSH), Thyroxine (fT4) and Tri-iodothyronine (fT3) was estimated by Access 2 Beckman Coulter CLIA analyser following the IFCC recommended guidelines at Central Laboratory, National Medical College. The laboratory assays was standardized and performed identically throughout the process.The data obtained were entered in Microsoft Excel sheet and analyzed by using the Statistical Package for the Social Sciences (SPSS) version 26. Descriptive statistic in the form of frequencies, percentages, mean, medians and standard deviations were used to describe the distribution and types of various thyroid hormone disorders. Chi-

square test and Fisher's exact test (to compare variable having frequencies less than 5) were used to calculate the significance between variables when applicable. $P < 0.05$ was considered statistically significant.

The normal reference range for thyroid function tests (TFT) in our laboratory is as follows: TSH 0.34-5.6 mIU/L, fT3: 2.5-3.9 pg/mL, and fT4: 0.61-1.12 ng/dL.

RESULTS

The study included majority of the cases (52%) belonging to the geriatric age group with the mean age of 57 years. The cases of male: female ratio was equal. [figure 1]. The most common condition encountered was lower respiratory tract infection (32%) followed by hypertension (31%), diabetes mellitus (26%), cerebrovascular accident (9%) and others (2%).

Majority of the study participants (42%) in APACHE II were from 20–24 across all participants, and both sexes and least participants (3%) had APACHE II score of above 34 [Figure 2].

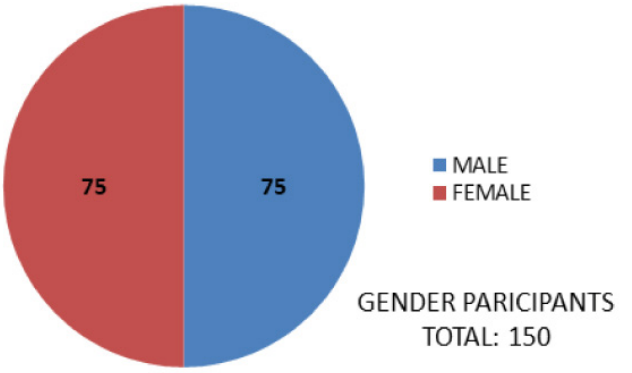

Figure 1: Distribution of cases according to gender

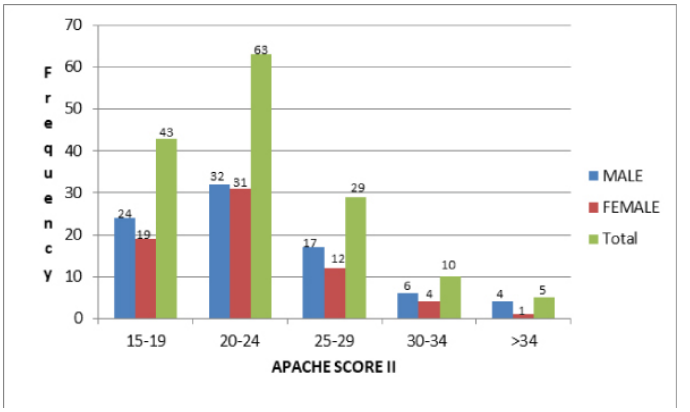

Figure 2: Distribution of cases according to APACHE II Score

Fiftyone percent of the patients had reduced fT3 levels followed by normal fT3 levels in 49% [Figure 3]. Seventynine percent of the patients had normal fT4 levels followed by reduced fT4 levels in 21% [Figure 4]. Eighty-one percent of the patients had normal TSH levels, followed by increased TSH levels in 13% and reduced TSH in only 6%. [Figure 5] No significant differences in the distribution of fT3, fT4, and TSH levels were found between males and females.

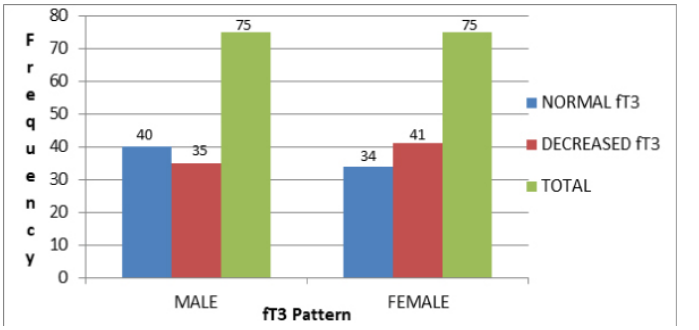

Figure 3: Distribution of patients as per free tri-iodothyronine levels

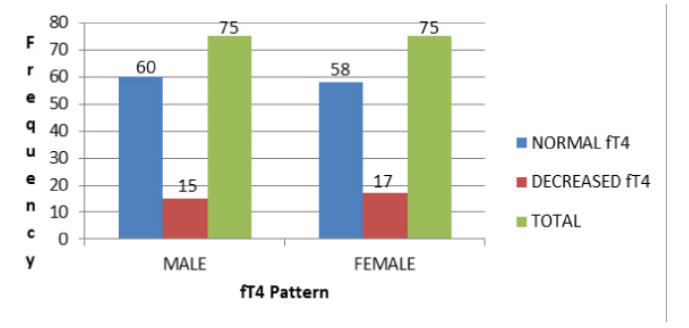

Figure 4: Distribution of patients as per free thyroxine levels

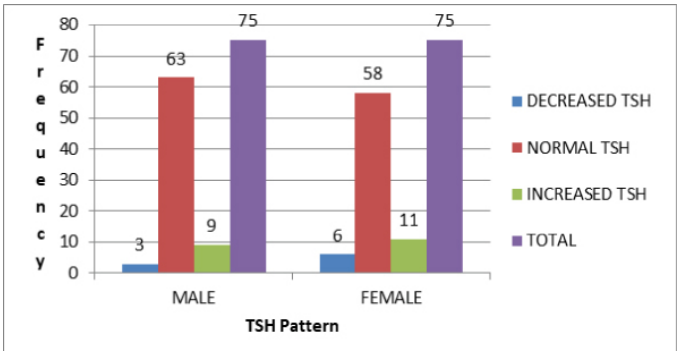

Figure 5: Distribution of patients as per TSH levels

There was an increase in percentage of patients with decreased fT3 levels with increasing APACHE Score II, compared to normal fT3 levels at similar APACHE II

score and the distribution was found to be statistically significant (Chisquare for trend with 1 degree of freedom; P = 0.0233), and cases of normal fT3 levels had increased survival compared to cases with decreased fT3 levels which was also statistically significant (twosided P < 0.0001, Fisher's exact test with Yates correction) [Table 1]. With increasing APACHE II Score, the distribution of cases with normal and decreased fT4 levels was similar in trend (Chisquare for trend with 1 degree of freedom; P = 0.6409), with no significant difference in fT4 levels between cases of survived and non-survived group (P = 0.8001, Fisher's exact test with Yates correction)[Table 2].

Table 1: Distribution of fT3 as per APACHE II score and outcome

APACHE SCORE II	Decreased fT3 (n)	Normal fT3 (n)
15-19	20	22
20-24	22	36
25-29	19	12
30-34	5	3
>34	10	1
Total	76 (24 survived and 52 expired)	74 (58 survived and 16 expired)

Table 2: Distribution of fT4 as per APACHE II score and outcome

APACHE SCORE II	Decreased fT4 (n)	Normal fT4 (n)
15-19	7	36
20-24	12	47
25-29	7	21
30-34	3	10
>34	4	3
Total	33 (19 survived and 14 expired)	117 (63 survived and 54 expired)

Table 3: Distribution of TSH AS per APACHE II score and outcome

APACHE SCORE II	Decreased TSH (n)	Normal TSH (n)	Increased TSH (n)
15-19	2	33	9
20-24	4	48	6
25-29	3	23	3
30-34	0	11	3
>34	0	5	0
Total	9 (2 survived and 7 expired)	120 (64 survived and 56 expired)	21 (16 survived and 5 expired)

The distribution of patients with increased, normal, and reduced TSH levels was similar in trend with increasing APACHE II score (for decreased TSH: Chisquare for trend with 1 degree of freedom; P = 0.8003 and for increased TSH: Chisquare for trend with 1 degree of freedom; P = 0.4001), with no significant difference in TSH levels between patients of survived and non-survived group (for decreased TSH: P = 0.1008, Fisher's exact test with Yates correction and for increased TSH: P = 0.1401, Fisher's exact test with Yates correction) [Table 3].

DISCUSSION

In severe and chronic illness, the thyroid hormone levels shows the characteristic discordant results, termed as Non-thyroidal illness syndrome or low T3 syndrome. It is considered to be caused by the inhibition of 5deiodinase enzyme by various mechanisms which actually catalyses T4 to T3 conversion.[5,6] In acute or severe illness, the usual changes seen are low T3 with increased T4 and rT3. But in a condition of chronic illness, low levels of T3, T4, and TSH are seen.[7,8]

A total of 150 cases with 75 males and 75 females were the participants of this study with average APACHE II score of 23.1. Lower respiratory tract infection was the most common cases of the study followed by hypertension, diabetes mellitus and cerebrovascular accidents. No significant difference in the thyroid profile among different diseases.

In a regular follow up, a total of 68 cases (about 45%) did not survive which is quite higher than the studies.[5,18,19] The reason may be that this is only tertiary care centre in this locality. No significant difference was seen in mortality between the gender groups. Isolated fT3 decrease were seen in 41 cases which is much higher in comparison study done in Sikkim in 2021 and only 10 patients were with isolated fT4 decreased levels.[20]

Thyroid hormone levels comparison of our study with other studies,[5,18,19] showed similar distribution pattern except that for TSH which was increased. However, it was comparable with the study done in Sikkim[20] [Table 4]. The reason may be due to the lack intake of iodinated salt and geographical location.

Of the 68 patients who expired, 52 of them had low fT3 levels whereas only 16 expired with the normal fT3 level. Thus, low fT3 is a very strong predictor of outcome in critically ill patients with P = 0.0001. There was an increase in percentage of patients with decreased fT3 levels with increasing APACHE Score II, compared to normal fT3 levels at similar APACHE II score and the distribution was found to be statistically significant (Chisquare for trend with 1 degree of freedom; P = 0.0233). The result was similar to the study done in Sikkim in 2017.

Studies	Zargar AH et al	K.V.S Hari Kumar et. al	Suresh et. al	Wang et.al.	Present study
% of low fT3	45	61	49	4.79	51
% of low fT4	16.7	16	22	11.4	22
% of TSH dysfunction	13.4	7	20	3.54	20

Table 4: Comparison of thyroid function tests among different studies and present study

Thirty-three patients were found with the low fT4 levels but less than half (n=14) of them only. Expired. This suggests that fT3 stands out to be the more prognostic indicator for outcome assessment of critical illness. This result was again comparable with the study done in Sikkim in 2017.[20] Similarly, TSH also has no significance in predicting the outcome of critical illness.

CONCLUSION

Decrease in the levels of fT3, a condition of non-thyroidal illness, is a crucial prognostic indicator in critically ill patients which in coordination APACHE Score II can be helpful in clinical settings to predict the severity and outcome of such patients. The result of the study will be helpful in determining the thyroid picture of the critically ill patients in our setting and definitely help in assessing the outcome of the patient admitted in ICU or ward.

ACKNOWLEDGEMENTS

ICU staffs and Laboratory staffs of National Medical College Teaching Hospital, Birgunj, Nepal.

CONFLICTS OF INTEREST: None

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