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Measurment of Thyroid Profile in Patients with Sepsis and its Association with Mortality

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Abstract

Background: Sepsis is an extremely common and a highly lethal condition. Sepsis is the foremost cause of deaths and critical illnesses world over. One of the most frequently involved systems in sepsis is the Endocrine system. The most common thyroid abnormality in sepsis is Euthyroid sick syndrome (ESS). Therefore, this study aimed to measure the levels of Thyroid hormone and assess their relationship with mortality in patients of sepsis. **Material and Methods:** This is a cross-sectional observational study conducted at ABVIMS & Dr. Ram Manohar Lohia Hospital, New Delhi- Intensive Care Unit, Emergency and Medicine ward from the duration of 1st January 2021-31st May 2022 with the sample size of 100 diagnosed cases satisfying the inclusion-exclusion criteria admitted in Department of Medicine. The analysis was done with the use of Statistical Package for Social Sciences (SPSS) software, IBM manufacturer, Chicago, USA, version 25.0 with the p-value<0.05 was considered statistically significant. **Results:** Total of 100 patients, majority were females (58%) with the age-group of 51-60 years. The mean value of qSOFA of study subjects was 2.51 ± 0.54 with median (25th-75th percentile) of 2(2-3) and range 2-4. Most commonly, the source of sepsis was found to be UTI (27%) > LRTI (18%) > septicaemia (11%). Statistically significant association was found between thyroid profile and the outcome (p-value<0.5). **Conclusion:** Incidence of sepsis is more common in older age and female gender. Older age, high qSOFA score is associated with increased mortality in patients with sepsis. UTI > LRTI are the most common source of sepsis. Low free T3 levels is most common abnormality in patients with sepsis. (90% patients). There is a positive correlation between low TSH level and decreased survival in patients with sepsis. Hence, TSH may be used as a predictor of mortality.

Keywords: Sepsis, Thyroid levels, qSOFA score, Euthyroid sick syndrome (ESS)

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Introduction

Sepsis is an extremely common and a highly lethal condition. Sepsis is the foremost cause of deaths and critical illnesses world over.[1,2] Over the past millennia, many attempts have been made to define sepsis. Initially thought of as an event required for wound healing and sometimes described as 'blood poisoning', it was in 1991 that it was defined as an inflammatory response to infection.[3] However, sepsis is a syndrome in which infection causes physiologic, pathologic and biochemical abnormalities. Sepsis develops when the initial appropriate response of the host body to infection becomes amplified. Clinically, its mostly insidious in onset, and may has presenting features such as: fever, transient hypotension, decreased urine output, unexplained thrombocytopenia etc.[4,5]

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Recent studies suggest incidence of around 3 cases per 1000 population. The overall mortality is around 30%, increases to around 40% in geriatric population, and is 50% or more in those who develop profound septic shock.[6] Sepsis affects almost every organ and organ system. One of the most frequently involved systems in sepsis is the Endocrine system.[7] When we look at neuroendocrine response of body to critical illness (i.e., sepsis), strong activation of parts of anterior pituitary function occurs and an inactivation of anabolic pathways in periphery. This in turn helps in providing metabolic substrates to support defence mechanisms of host, same as "fight or flight" reaction. The most common thyroid abnormality in sepsis is Euthyroid sick syndrome (ESS). It is described as abnormalities in circulating thyroid hormone levels without any pre-existing hypothalamic, pituitary or thyroid gland dysfunction in the setting of non-thyroidal illness.[8,9] Therefore, this study aimed to measure the levels of Thyroid hormone and assess their relationship with mortality in patients of sepsis.

Methodology

Study place: ABVIMS & Dr. Ram Manohar Lohia Hospital, New Delhi- Intensive Care Unit, Emergency and Medicine ward.

Study design: Cross-sectional observational study

Study period: 1st January 2021-31st May 2022

Sample size: 100 diagnosed cases satisfying the inclusion-exclusion criteria admitted in Department of Medicine.

Inclusion Criteria

- Patients of age 18 years or above.
- Sepsis or Septic Shock, diagnosed according to the Society of Critical Care Medicine criteria, third international consensus Definition for sepsis and septic shock (sepsis-3) 2016., considering the qSOFA and the SOFA scores.

Exclusion criteria

- Patients with known thyroid disease
- Patients taking thyroid replacement therapy or anti-thyroid drugs
- Patients with pre-existing liver failure, renal failure and CAD.
- HIV + individuals on ART
- Pregnant females
- Patients with any malignancy

Technique

- After obtaining the written informed consent, details of the patient, such as age, gender, Body Mass Index (BMI), underlying diseases and co-morbidities was noted.
- The severity of illness was evaluated according to the SOFA score, described in the Sepsis 3 definition. Acute Physiology and Chronic Health Evaluation II (APACHE II) score, was determined in all patients within the first 24 hours of hospital admission and the inclusion and exclusion criteria were thoroughly assessed.

The following baseline investigations were sent within 24 hours of admission:

- Complete hemogram
- Liver Function Tests (Bilirubin, SGOT, SGPT, Alkaline Phosphatase, Total Protein, Albumin, Globulin)
- Renal Function Tests (Urea, Creatinine, Uric Acid)
- Serum Electrolytes (Na+, K+, Ca2+, PO43-, Mg2+)

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- Serum C Reactive Protein (CRP), Ferritin, Procalcitonin, Lactate.
- Coagulation profile (PT, INR, aPTT) to look for coagulopathy and DIC.

The source of infection was searched using:

- Cultures of blood, urine, endotracheal / tracheostomy tube secretions, sputum or any secretions from any wound site.
- Imaging: Xray, ultrasound, CT scan, MRI.
- The need, duration of Mechanical Ventilation (MV) and weaning off the ventilator will also be assessed in the sepsis patients.

Assessment of Thyroid status:

- 2-3 ml venous blood was collected in PLAIN vial within 24 hours of admission to the hospital.
- Sample was sent to Biochemistry lab for measurement of Free T3, Free T4 and TSH via chemiluminescent assay.

Patient was then followed to see end outcome-survivor/non-survivor, i.e., discharge/death from the hospital.

Sample size calculation

Our estimated sample size was based on to compare FT3 in survivors and non survivors. With reference to previous study (Pal A, Jain N, Patidar M. Study of Thyroid Profile in Patients with Sepsis),[10] the mean FT3 was 1.56 with SD 0.77 in Non survivors and mean FT3 was 2.31 with SD 0.65 in survivors. Thus, sample size of 18 patients per group provided an 90% power for detecting a significant difference between two groups at an alpha level of 0.05 one sided. Since the mortality rate was 37.3%, therefore we took 100 patients in total.

The formula for calculated sample size is given below:

$$n = \frac{(\sigma 1^2 + \sigma 2^2).\,[Z\ 1-\alpha/2 + Z\ 1-\beta]^2}{(M1 - M2)^2}$$

$$= \frac{(0.77^2 + 0.65^2).\,[1.96+1.282]^2}{(0.75*0.75)}$$

$$= \frac{(0.593+ 0.423)\ *10.51}{0.563}$$

$$= 18.973$$

where $Z_{\alpha/2}$ is the critical value of the Normal distribution at $\alpha/2$ (e.g., for a confidence level of 95%, α is 0.05 and the critical value is 1.96), Z_β is the critical value of the Normal distribution at β (e.g., for a power of 90%, β is 0.1 and its critical value is 1.282) and σ 1 and σ 2 are the Standard deviations of the two groups and M1 and M2 are the means of two groups.

Statistical analysis

The presentation of the Categorical variables was done in the form of numbers and percentage (%). On the other hand, the quantitative data was presented as the mean ± SD and as the median with 25th and 75th percentiles (interquartile range). The data normality was checked by using Kolmogorov-Smirnov test. The cases in which the data was not normal, non-parametric tests were used. The association of the variables which were quantitative and not normally distributed in nature were analysed using Mann-Whitney Test (for two groups) and independent t test was used for association of the variables which were quantitative and normally distributed. The association of the variables which were qualitative in nature were analysed using Chi-Square test. If any cell had an expected value of less than 5, then Fisher's exact test was used. The data entry was done in the Microsoft EXCEL spreadsheet and the

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final analysis was done with the use of Statistical Package for Social Sciences (SPSS) software, IBM manufacturer, Chicago, USA, version 25.0. For statistical significance, p-value<0.05 was considered statistically significant.

RESULTS

Table 1: concluded that, out of total 100 patients, majority (58%) were females, and 42% were males.

Sex	N	%
Female	58	58%
Male	42	42%
Total	100	100%

[Figure 1] represents the mean value of age (in years) of study subjects was 59.13 ± 17.3 with median (25th-75th percentile) of 59 (45-72). Maximum of the age-group belong to 51-60 years, with least to 21-30 years, and >90 years, respectively.

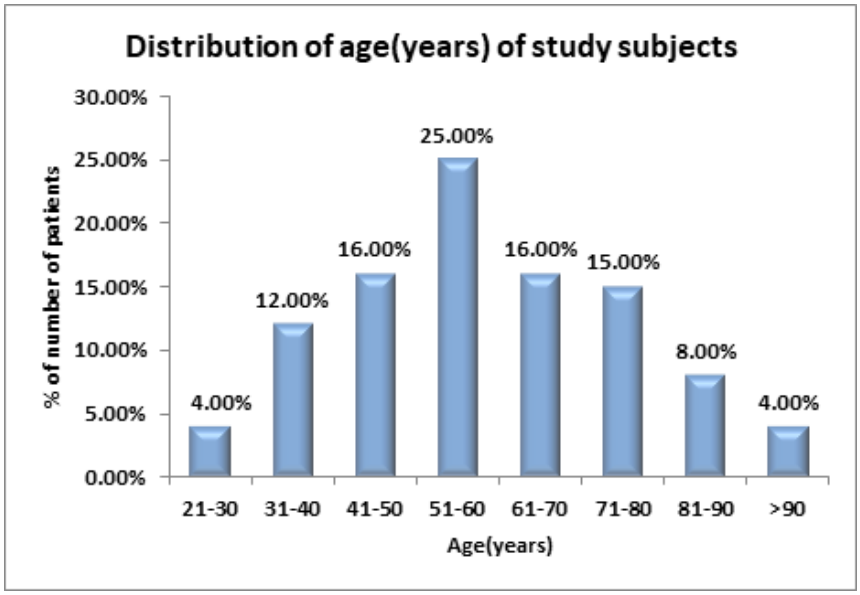

Figure 1: Distribution of study participants according to age-group (years).

[Figure 2] indicated the mean value of qSOFA of study subjects was 2.51 ± 0.54 with median (25th-75th percentile) of 2(2-3) and range 2-4.

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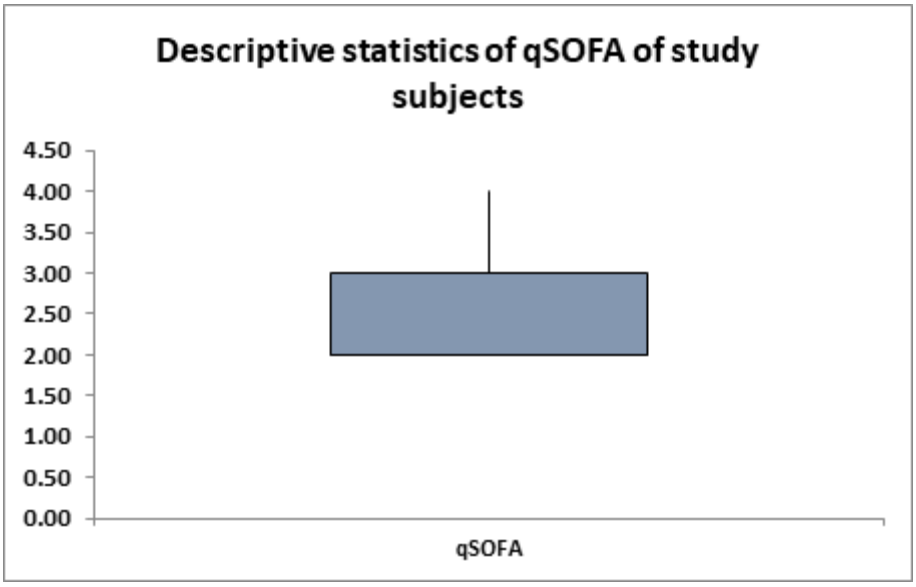

Figure 2: Descriptive statistics of qSOFA of study subjects

Table 2: Distribution according to Thyroid Profile (uIU/mL) of study participants.

TSH (uIU/mL)	**N (%)**
Low TSH {<0.34 uIU/mL}	7 (7%)
Normal TSH {0.34 to 5.6 uIU/mL}	78 (78%)
High TSH {>5.6 uIU/mL	15 (15%)
Mean ± SD	3.63 ± 3.75
Median (25th-75th percentile)	2.9(1.7-4.56)
Range	0.09-32.16
FT3(pg/mL)	N (%)
Low fT3{<2.5 pg/mL}	90 (90%)
Normal fT3 {2.5 to 3.9 pg/mL}	6 (6%)
High fT3{>3.9 pg/mL	4 (4%)
Mean ± SD	1.54 ± 1.24
Median (25th-75th percentile)	1.31(0.775-1.928)
Range	0.09-10.5
FT4(ng/dL)	N (%)
Low fT4{<0.61 ng/dL}	18 (18%)
Normal fT4 {0.61 to 1.12 ng/dL}	20 (20%)
High fT4{>1.12 ng/dL	62 (62%)
Mean ± SD	2.57 ± 2.97
Median (25th-75th percentile)	1.32(0.8-3.775)
Range	0.01-19.7

In the present study, 78% of patients had normal TSH (0.34 to 5.6 uIU/mL), 15% had high TSH (>5.6 uIU/mL), and 7% had low TSH (<0.34 uIU/mL}). With Free T3 level, 90% of patients had low fT3 (<2.5 pg/mL), 6% had normal fT3 (2.5 to 3.9 pg/mL), and 4% had high fT3 (>3.9 pg/mL). In FT4 level, 62% of patients had high fT4 (>1.12 ng/dL), 20% had normal fT4 (0.61 to 1.12 ng/dL), and 18% had low fT4 (<0.61 ng/dL).

In [Figure 3], higher extent belongs to the outcome of discharge (56%), and 44% to the mortality.

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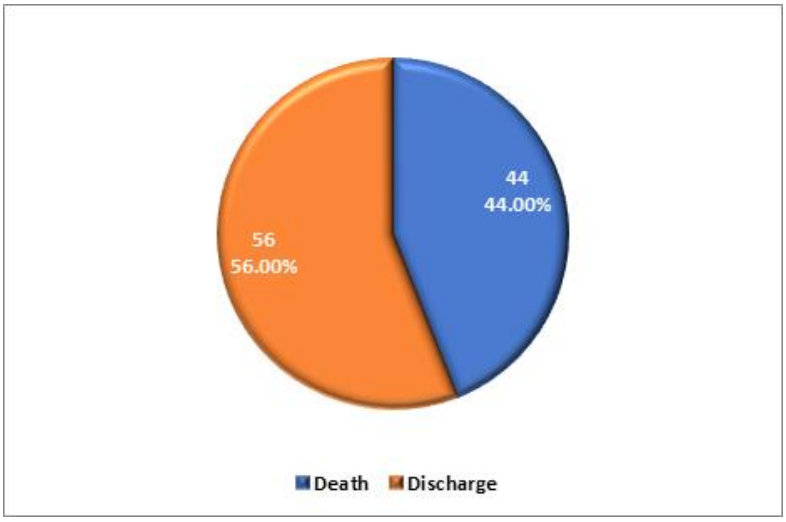

Figure 3: Distribution of study participants in terms of the outcome in the study

Table 3: Association of qSOFA with Outcome.

qSOFA	Death(n=44)	Discharge(n=56)	Total	P value
Mean ± SD	2.66 ± 0.53	2.39 ± 0.53	2.51 ± 0.54	0.014‡
Median (25th-75th ercentile)	3 (2-3)	2(2-3)	2(2-3)	
Range	2-4	2-4	2-4	

‡ Independent t test

[Table 3] reported the mean ± SD of qSOFA in patients who died was 2.66 ± 0.53 which was significantly higher as compared to patients who were discharged (2.39 ± 0.53). (p value=0.014).

Table 4: Association of Thyroid profile (uIU/mL) with outcome.

TSH (uIU/mL)	Death(n=44)	Discharge(n=56)	Total	P value
Low TSH {<0.34 uIU/mL}	6 (85.71%)	1 (14.29%)	7 (100%)	0.042*
Normal TSH {0.34 to 5.6 uIU/mL}	31 (39.74%)	47 (60.26%)	78 (100%)	0.106†
High TSH {>5.6 uIU/mL	7 (46.67%)	8 (53.33%)	15 (100%)	0.821†
Mean ± SD	2.93 ± 2.46	4.17 ± 4.47	3.63 ± 3.75	0.047§
Median (25th-75th percentile)	2.35 (1-4.6)	3.2 (2.4-4.56)	2.9 (1.7-4.56)	
Range	0.09-9	0.1-32.16	0.09-32.16	
FT3(pg/mL)	Death(n=44)	Discharge(n=56)	Total	P value
Low fT3{<2.5 pg/mL}	41 (45.56%)	49 (54.44%)	90 (100%)	0.506*
Normal fT3 {2.5 to 3.9 pg/mL}	1 (16.67%)	5 (83.33%)	6 (100%)	0.225*
High fT3{>3.9 pg/mL	2 (50%)	2 (50%)	4 (100%)	1*
Mean ± SD	1.67 ± 1.55	1.43 ± 0.94	1.54 ± 1.24	0.376§
Median (25th-75th percentile)	1.44 (1.072-1.962)	1.1 (0.76-1.905)	1.31 (0.775-1.928)	
Range	0.12-10.5	0.09-4.5	0.09-10.5	
FT4(ng/dL)	Death(n=44)	Discharge(n=56)	Total	P value
Low fT4{<0.61 ng/dL}	6 (33.33%)	12 (66.67%)	18 (100%)	0.314†
Normal fT4 {0.61 to 1.12 ng/dL}	10 (50%)	10 (50%)	20 (100%)	0.546†
High fT4{>1.12 ng/dL	28 (45.16%)	34 (54.84%)	62 (100%)	0.765†
Mean ± SD	1.92 ± 2.06	3.08 ± 3.46	2.57 ± 2.97	0.468§
Median (25th-75th percentile)	1.33 (0.9-1.74)	1.31 (0.755-4.862)	1.32 (0.8-3.775)	
Range	0.15-10.89	0.01-19.7	0.01-19.7	

§ Mann Whitney test, * Fisher's exact test, † Chi square test

Proportion of death was significantly higher in patients with low TSH (85.71%) as compared to patients with normal TSH (39.74%) or high TSH (46.67%). (p value=0.042). Median

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(25th-75th percentile) of TSH in discharged patients was 3.2(2.4-4.56) which was significantly higher as compared to patients who died (2.35(1-4.6)). (p value=0.047).
Median (25th-75th percentile) of fT3(pg/mL) in patients who died was 1.44(1.072-1.962) and patients who were discharged was 1.1(0.76-1.905) with no significant association between them. (p value=0.376). Distribution of mortality was comparable with fT3 values of all 3 groups. (Low fT3{<2.5 pg/mL} (45.56%) vs Normal fT3 {2.5 to 3.9 pg/mL} (16.67%) vs High fT3{>3.9 pg/mL (50%)). (p value=0.506).
Median (25th-75th percentile) of fT4 in patients who died was 1.33(0.9-1.74) and discharged was 1.31(0.755-4.862) with no significant association between them. (p value=0.468). Distribution of mortality was comparable with fT4 values of all 3 groups (Low fT4{<0.61 ng/dL} (33.33%) vs Normal fT4 {0.61 to 1.12 ng/dL} (50%) vs High fT4{>1.12 ng/dL (45.16%)). (p value=0.314).

DISCUSSION

A cross sectional study was conducted in the Department of Medicine, Atal Bihari Vajpayee Institute of Medical Sciences & Dr Ram Manohar Lohia Hospital from 1st January 2020 to 31st May 2022 to know the prognostic significance of thyroid hormone levels in patients with sepsis. A total of 100 patients aged 18 years and above taken, as per the inclusion and exclusion criteria decided in the protocol. Sepsis is a significant health burden globally and causes considerable morbidity and mortality. Early identification, effective decision making and early start of therapy can be lifesaving in such patients, and therefore present study was undertaken.
A total of 100 patients were included in the study. Age of the study subjects ranged from 23 to 93 years, mean value of age(years) of study subjects was 59.13 ± 17.3 with median (25th-75th percentile) of 59(45-72). Majority of the patients in the study belonged to 51-60 years of age, and thus showing increasing incidence of sepsis with advancing age. This is similar to that in study done by Padhi R et al.[11] Moreover, out of 100 patients, 58 were females and 22 were males. Female patients are at higher risk of sepsis. This is in in accordance to study done by Ghanshani et al.[12] Additionally, with the outcome profile, 44 patients had died, while 56 were discharged. This is similar to patient outcome in study done by A. Pal et al.[10] The most common source of sepsis in the present study was UTI (27%) followed by LRTI (18%). This is in contrast to study done by Chaterjee S. et al, where they found most common source of sepsis in inpatients to be infections involving respiratory tract, mostly Pneumonia and the most common microbe responsible in this study was Acinetobactor baumanni.[13]

Thyroid hormone levels in patients

In present study, Mean value of TSH (uIU/mL) of study subjects was 3.63 ± 3.75 with median (25th-75th percentile) of 2.9(1.7-4.56). Out of 100 patients, 78% of them had normal TSH, followed by high in 15% of patients. TSH was low in only 7% of patients. These findings are similar to those in study by Padhi et al, where around 75% of patients had normal TSH values.[11] TSH levels are deranged in patients usually in later stages, initially there is fall in level of T3 or T4 without changes in TSH.
On measuring Free T3 levels in patients of present study, 90% of patients had low FT3 levels. Mean value of FT3(pg/mL) of study subjects was 1.54 ± 1.24 with median (25th-75th percentile) of 1.31(0.775-1.928)., that was also below normal. This is similar to findings of study done by A. Pal et al, Lodhi et al, Mangas-Rojas et al; which showed that low FT3 was the commonest abnormality in thyroid profile in patients with sepsis.[10,14,15] Thyroid hormone is secreted by thyroid gland as T4 (80%) and T3 (20%), while T3 is the active form of hormone which acts on peripheral receptors. T4 forms T3 by 5'deiodinase activity and it also clears reverse t3(rT3). In sepsis, there is inhibition of 5'deiodinase, and thus fall in level of T3 and increase in level of inactive rT3 occurs. On measuring Free T4 levels, majority of

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patients (62%) had high FT4, followed by normal in 20% of patients and low in 18% of patients. This were in contrast to findings found by A. Pal et al and Padhi et al,[10,11] where they found that majority of patients with sepsis had low FT4 followed by normal FT4, while high FT4 was present in about only 10% of patients.

Association of qsofa with outcome

In present study, mean ± SD of qSOFA in died patients was 2.66 ± 0.53 which was significantly higher as compared to discharged (2.39 ± 0.53). This had a significant p value=0.014. This is in accordance to finding in study done by Yu H. et al, which showed that higher qSOFA score is a predictor of mortality in patients with sepsis.[16]

Association of source of sepsis with outcome

Mortality rate was significantly higher in patients with Aspiration pneumonitis (100%, p value=0.035) and was significantly lower in patients with UTI (25.93%, p value=0.027). This is in accordance to study done by Brun-Buisson C. et al,[17] which showed that patients with multiple comorbidities were more prone to sepsis, and the mortality increased in patients with more severe infection.

Association of Thyroid profile with outcome

In present study, Proportion of death was significantly higher in patients with low TSH (85.71%) as compared to patients with normal TSH (39.74%) or high TSH (46.67%). It was statistically significant with p value=0.042. This is similar to findings in study done by Lodha et al, only TSH was found to be significantly lower in survivors TSH in survivors versus non-survivors was 0.26 (0.22–0.88) versus 1.21 (0.27–2.96) μIU/mL (P = 0.04).[14] And in Euthyroid sick syndrome, patients with low severity of illness may have normal TSH, and with increasing severity of illness, a greater number of patients had low TSH values, representing a continuum in illness. Thus, patients with low TSH values have increased risk of mortality as shown in study by Umpierrez Guillermo E.[9] Median (25^{th}-75^{th} percentile) of TSH in discharged patients was 3.2(2.4-4.56) which was significantly higher as compared to patients who died (2.35(1-4.6)), with statistically significant p value of 0.047. Thus, survivor patients had higher TSH values as compared to non-survivors.

In present study, median (25th-75th percentile) of FT3(pg/mL) in non-survivors was 1.44(1.072-1.962) and survivors was 1.1(0.76-1.905) with no significant association between them. It has p value=0.376. This is in contrast to study done by A. Pal et al and Mangas-Rojas et al, in which non-survivors had low mean FT3 (1.56 ± 0.77) than survivors (2.31 ± 0.65) which was statistically significant (p <0.0001). [10, 15] Distribution of mortality was comparable with FT3 values of all 3 groups. (Low FT3{<2.5 pg/mL} (45.56%) vs Normal FT3 {2.5 to 3.9 pg/mL} (16.67%) vs High FT3{>3.9 pg/mL (50%)). It is statistically non-significant with p value=0.506. These finding were consistent with study done by Meyer et al, which showed that there was no difference in T3 and fT4 on admission in non-survivors compared with survivors.[18]

In our study, median (25^{th}-75^{th} percentile) of FT4 in patients who died is 1.33(0.9-1.74) and patients who are discharged is 1.31(0.755-4.862) with no significant association between them, with p value=0.468. Distribution of mortality was comparable with FT4 values of all 3 groups (Low FT4{<0.61 ng/dL} (33.33%) vs Normal FT4 {0.61 to 1.12 ng/dL} (50%) vs High FT4{>1.12 ng/dL (45.16%)). It is statistically insignificant with p value of 0.314. It is consistent with findings in study done by Meyer et al, which showed that FT4 decreased significantly in non-survivors on follow-up and non-survivors had low FT4 compared to survivors on their day of death.[18] While the findings were consistent with those by Lodha et al, which showed that there was no significant difference in FT4 values at the time of admission, in patients who died or survived.[14]

CONCLUSION

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Low free T3 levels is most common abnormality in patients with sepsis. (90% patients). There is a positive correlation between low TSH level and decreased survival in patients with sepsis. Hence, TSH may be used as a predictor of mortality. However, no significant correlation found between free T3 and free T4 levels with mortality. Therefore, they can't be used as predictors of mortality.

Limitations

This study was a cross-sectional study with small sample size of 100, therefore required further research with large number of cases to generalize the findings. Thyroid hormone levels were measured only at the time of admission, and patients were followed up for a shorter duration of time during the hospital stay. Studies with longer follow-up period to assess 28-days and 90-days mortality required for generalization which is not possible in the current study, moreover, qSOFA is used for the identification of sepsis. This may lead to overestimation or underestimation of the disease magnitude. Thus, intensive exploration with critical illness other than sepsis is required to use thyroid profile as a predictor of the mortality in ICU patients.

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