STUDY TO ASSESS THE RELATIONSHIP BETWEEN THYROID STATUS AND ITS ASSOCIATION WITH OUTCOME IN PATIENTS WITH SEPSIS

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ABSTRACT

Sepsis is defined as life-threatening organ dysfunction due to dysregulated host response to infection. Mortality due to sepsis is more than 30%. Early identification and early goal directed therapy in sepsis are important for good outcome. Here in this study we are trying to assess the thyroid function test and its association with clinical outcome in sepsis patients. The objective is to assess the thyroid function test among the patients presenting with sepsis. This is a Prospective study that included 70 patients admitted in Chettinad Hospital And Research Institute with sepsis. Low FT3 levels correlated significantly with the primary outcome with a cut off value of <1.13pg/ml. All the three thyroid function test (FT3, FT4, TSH) had a significant correlation with the primary and secondary outcome in subjects with sepsis. Low FT3 levels can be considered as a single independent predictive mortality marker in subjects with sepsis. Raised TSH levels can be considered as a predictive marker for requirement of ionotropic support in subjects with sepsis. In patients with Low FT4 Levels interventional procedure requirement is high.

KEY WORDS: Thyroid hormone, sepsis, triiodothyronine

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INTRODUCTION

Thyroid hormone plays an important role in metabolic function adaptation to stress and critical illness mainly sepsis. Predicting the sepsis outcome even before obtaining culture, depending on thyroid profile may help in starting early efficient treatment and improve the prognosis of patients \(^1\). Sepsis is the life threatening organ dysfunction due to dysregulated host response to infection. Mortality due to sepsis is more than 30\% and septic shock remains the common cause of death in ICU setup \(^2\). Early identification and early goal directed therapy in sepsis are important for good outcome. Various biomarkers are available to detect the outcome and severity of sepsis. One among them is thyroid hormone levels. Thyroid hormone plays a unique role in metabolic function adaptation to stress and critical illness mainly sepsis. Several inflammatory cytokines can suppress thyroid function at different levels and in sepsis the production of pro-inflammatory cytokines are more when compared to other types of critical illness. Various patterns of thyroid function abnormalities affect the severity of sepsis \(^3\). In patient with sepsis, thyroid dysfunctions are transient and not a true thyroid disorder. But, few data suggests that the various thyroid hormone abnormalities in sepsis due to different causes associated adversely with the patient outcome. This study was conducted to assess the prognostic value of the thyroid function test (FT3, FT4, and TSH) and its association with clinical outcome in terms of mortality and requirement of ventilator support, ionotropic support and interventional procedure in subjects with sepsis. Provide references for the introduction

MATERIAL AND METHODS STUDY DESIGN:

This is a Prospective observational study. Patients with sepsis attending emergency department or admitted to intensive care unit (ICU) of Chettinad Hospital and Research Institute, Kelambakkam, Chennai, TN, India.

DATA COLLECTION:

Informed consent was taken from all subjects and in case of unconscious subjects from the relatives. Blood samples were drawn at time of admission before initiation of treatment and were processed within 30 minutes of collection using an autoanalyser. Analysis of serum free triiodothyronine, free thyroxine and thyroid stimulating hormone were done using chemo-luminescence immunoassay (CLIA) technique. Demographic data, the presenting symptoms along with comorbidities were recorded for all the subjects.
History was taken pertaining to symptoms of sepsis. Detailed clinical examination was done for all subjects. Qsofa scoring has been done to diagnose the patients with sepsis. Primary and secondary outcome was assessed.

**DISCUSSION** Provide references in the discussion and do a comparison of your study with other studies if any

Early goal directed therapy is the first important step to be done in sepsis management, along with administration of broad spectrum antibiotics and mechanical ventilation, if required. Guidelines suggest emergency care for early stage of sepsis (within 6 hours) \(^4\). But the problem is deciding which group of patients will need escalation or deescalation of antibiotics or who will need mechanical ventilation or ionotrope support. To know the severity in sepsis there are various scoring systems available like qSOFA done outside the ICU, SOFA scoring done in ICU.

In the study we have assessed the relationship between thyroid function test (FT3, FT4, TSH) and its association with outcome in patient with sepsis. There are only limited data regarding abnormality of thyroid function during sepsis and most of the Indian studies were about thyroid dysfunction in critically ill conditions \(^5\). Since sepsis is one of the leading contributor of in hospital mortality, this study has been done. If such relationship exists then an interventional study which may prove the correction of thyroid levels will improve the outcome of sepsis may be considered.

Totally 70 sepsis patients were enrolled for the study. Qsofa scoring done to diagnose the patient with sepsis. Thyroid dysfunctions were found out in the study population and were put in to six groups as subclinical hypothyroid, subclinical hyperthyroid, overt hypothyroid, low ft3 levels, low ft3, ft4 levels. Individual values of thyroid function test (ft3, ft4, tsh) were assessed for study population. Based on the primary outcome, they were further divided into two groups as survivors and non survivors. Secondary outcome (requirement of mechanical ventilation, ionotropic support and interventional procedure) of the study population was correlated with age, sex and risk factors.

**DEMOGRAPHICS:**

In the study 57.14% of the study group were men i.e. 40 male patients with the remainder 30 being female patients (42.86% of the study population).

According to the age, minimum age observed was 18yrs and maximum age was 83yrs with majority of the patients were in the age group between 41 and 60 yrs, 37 patients (52.86% of study population). Present study indicated that

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there was no significant correlation between age, sex and outcome in patient with sepsis. This was similar to studies done by Angus et al., which concluded, although the chances of developing sepsis differed for men and women by age, the likelihood of dying from sepsis was the same for men and women after adjusting for age, underlying comorbidity, and site of infection\(^6\).

qSOFA:

Finkelsztein et al., in his study with 152 patients in sepsis has stated that, the in-hospital mortality of qSOFA-positive patients was higher than that of qSOFA-negative patients (27% vs 6%; \(p < 0.01\)) \(^7\). The study has only qsofa scoring of 2 and 3 with majority having qsofa scoring of 2 in 51 patients (72.86% of the study population) Qsofa scoring of 3 were seen in 19 patients(27.14% of the study population)

RISK FACTORS:

In this study 70% of the study population had comorbidities i.e. 49 people of the study population. In that 15 people had diabetes(21.4% of the study population),3 had systemic hypertension(4.2% of the study population),31 people had combined diabetes and hypertension(44.28% of the study population). A metaanalysis done by Wang et al, based on 10 enrolled studies performed between 2000 and 2016 indicated that the mortality rate of septic patients with DM was slightly lower than that of non-diabetic patients (risk ratio [RR]=0.97, 95% confidence interval [CI]: 0.96 to 0.98,\(P<0.00001\)) \(^8\). In the study there were no correlation between comorbidities and outcome. Only 21 people didn’t have any comorbidities (30% of the study population)

THYROID FUNCTION TEST:

84.2% of the study population had thyroid dysfunction and were put in to six groups as subclinical hypothyroid, subclinical hyperthyroid, overt hypothyroid, low ft3 levels, low ft3, ft4 levels and normal thyroid status. Normal thyroid levels were found in 15.71% of the study population (n=11). Overt hypothyroid status were found in 11.43% of the study population (n=8). Subclinical hypothyroid were found in 20% of the study population (n=14) Subclinical hyperthyroid were found in 10% of the study population (n=7). Low ft3 levels were found in 31.43% of the study population (n=22). Low ft3, ft4 levels were found in 11.43% of the study population (n=8). Majority of the patients had low ft3 levels and second majority from subclinical hypothyroidism (raised tsh). Thyroid dysfunction was more in the age group between 41 and 60 yrs of age with male predominance.

PRIMARY OUTCOME: (SURVIVORS AND NON-SURVIVORS) BASED ON DEMOGRAPHY:
In this study, the patients were monitored throughout the in hospital stay and were divided into survivors and nonsurvivors. Among the 70 sepsis patient 14.29% (n=10) were non survivors and remaining 85.71 % (n=60) were survivors at the end of the study.

**Age distribution:**

In this study among the 70 sepsis patient, according to age distribution 40% (n=4) were between 41 and 60 yrs. 40% (n=4) were between 61 and 80 yrs. Remaining 20% (n=2) were between 21 and 40 yrs of the study population. When statistically comparing, age distribution between the primary outcome groups, the difference in the mean age of patients across the groups was found to be statistically non-significant (p >0.05).

**PRIMARY OUTCOME IN PATIENTS WITH THYROID DYSFUNCTION ASSOCIATED WITH SEPSIS:**

Kumar et al concluded that the low T3 is the marker of illness severity and predicts mortality in icu patients and the same was not seen when combining low T3 and low T4. In this study, the patients were monitored throughout the in hospital stay and were divided into survivors and nonsurvivors. Among the 70 sepsis patient 14.29% (n=10) were non survivors and remaining 85.71% (n=60) were survivors at the end of the study. Maximum number of sepsis patients were having low FT3 levels i.e. 31.43% (n=22).

Among the non survivors 14.29% (n=10), 12.86% (n=9) were having low FT3 levels remaining 1.43% (n=1) were having low FT3, FT4 levels. Significant P value of 0.040 was obtained which signifies that low FT3 levels had high chances of non survivors. Previous study involving pediatric ICU patients showed that low T3 is a better predictor of mortality and the risk of mortality is increased by 30 times when it is associated with low T4 levels. But this trend was not observed in our study, and this could be due to adult population in our study.

**SECONDARY OUTCOME IN PATIENTS WITH THYROID DYSFUNCTION ASSOCIATED WITH SEPSIS:**

Faiza et al concluded that there is no difference in the risk of patient getting mechanically ventilated based on their thyroid status function. But in our study The requirement of ventilator support were more among patients with low FT3 levels i.e. n=14 and second maximum is with subclinical hypothyroidism (n=13). Significant p value of 0.022 was obtained which implies that sepsis patient with thyroid dysfunction had high chances of requirement of
ventilator support with maximum frequency from low FT3 level patients. These results could be because of taking sepsis patients particularly.

The requirement of ionotrophic support were more among patient with subclinical hypothyroid status (n=13) and second maximum is with low FT3 levels (n=10). Significant p value of 0.027 was obtained which implies that sepsis patient with thyroid dysfunction had high chances of requirement of ionotrophic support with maximum frequency being subclinical hypothyroid patients.

The requirement of interventional procedure were more among patient with subclinical hypothyroid status (n=6) and second maximum is with low FT3 levels (n=5). P value was not significance in this case.

**ANALYSIS OF ACCURACY OF PRIMARY OUTCOME (NON SURVIVORS) AND THYROID FUNCTION TEST (FT3, FT4, TSH):**

Thyroid function test correlated with primary outcome with area under ROC curve of FT3-0.948. The AUROC curve showed, with a cut off of FT3 levels of 1.13, sensitivity and specificity was 94% and 83% respectively, with a statistical significance of (p<0.001) to predict the primary outcome. An excellent case finding or diagnostic test with high specificity and PPV suggesting that false positives are very rare. It is also a very good screening test with high sensitivity and NPV suggesting that high false negative tests will occur rarely. Previous study by Wang et al found that FT3 was the best among the thyroid function test for predicting ICU death, as it was suggested by the largest AUC of 0.762 (11).

**ANALYSIS OF ACCURACY OF SECONDARY OUTCOME (NEED FOR MECHANICAL VENTILATION, REQUIREMENT OF IONOTROPIC SUPPORT AND INTERVENTIONAL PROCEDURE) AND THYROID FUNCTION TEST (FT3, FT4, TSH):**

The AUROC curve showed a cut off of TSH levels of >5.12, sensitivity and specificity was 98% and 50% respectively, with a statistical significance of (p<0.005) for the requirement of ionotrophic support. A good case finding or diagnostic test with moderate specificity and PPV suggesting that false positives are very rare. It is also a very good screening test with high sensitivity and NPV suggesting that high false negative tests will occur rarely. On the whole it is a good combined diagnostic and screening tool with very high clinical utility to predict ionotrophic support need in sepsis patients.

The AUROC curve showed a cut off of FT4 levels of <0.52, sensitivity and specificity was 91% and 87% respectively, with a statistical significance of (p<0.04) for the requirement of interventional procedure. A good case
finding or diagnostic test with very high specificity and PPV suggesting that false positives are very rare. It is also a very good screening test with high sensitivity and NPV suggesting that high false negative tests will occur rarely. On the whole it is a good combined diagnostic and screening tool with very high clinical utility to predictive interventional procedure need in sepsis patients.

CONCLUSION

- All the three thyroid function test (FT3, FT4, and TSH) had a significant correlation with the primary and secondary outcome in subjects with sepsis.
- FT3 levels can be considered as a single independent predictive mortality marker in subjects with sepsis. FT3 estimation in patients with sepsis is a simple, rapid and inexpensive laboratory test. It can play a vital role as a corroborative investigation in prediction of mortality in sepsis.
- FT3 level cut off of <1.13 pg/ml has a sensitivity of 94% and specificity of 83% in predicting the mortality in subjects with sepsis.
- TSH levels can be considered as a predictive marker for requirement of ionotropic support in subjects with sepsis with a cut off value of >5.12 miu per L and it has a good sensitivity of 98%
- FT4 levels can be considered as a predictive marker for requirement of interventional procedure in subjects with sepsis with a cut off value of<0.52 ng per dl with a good sensitivity of 94%.
- Further studies are needed for establishing the facts of the current study and to design a study on the clinical outcomes among the sepsis patients receiving proper thyroid hormone replacement therapy.

REFERENCES


11. Eli J. Finkelsztein, Daniel S. Jones, Kevin C. M. Comparison of qSOFA and SIRS for predicting adverse outcomes of patients with suspicion of sepsis outside the intensive care unit. Critical Care, 2017, Volume 21, Number 1, Page.