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Prognostic Value of Thyroid Profile on Disease Severity and Mortality in COVID-19

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COVID-19; SARS-CoV-2; Thyroid hormone; TSH; Critically ill

1. Abstract

1.1. Background

Precise accurate triage of COVID-19 patients during hospitalization for early identification of individuals at risk of developing severe disease.

1.2. The Aim

Of this study was to evaluate thyroid function in patients with COVID-19.

1.3. Methods

Confirmed COVID-19 andnon-COVID-19 pneumonia patients (included as control group) admitted to cardiothoracic hospital, Minia University, Egypt, between March 2020 and Sept 2021without history of thyroid disease. We analyzed the ability of each parameter to predict mortality in participants. Further, evaluated whether the combination of FT3 level with APACHE-II score could improve the mortality prediction.

1.4. Results

TSH was lower than normal range in 56.7% (68/120) of patients with COVID-19. TSH and serum FT3 were significantly lower in-COVID-19 patients than healthy control and non-COVID-19 pneumonia patients. TSH and FT3 were lower in severe COVID-19 with statistical significance and both positively correlated with the severity. FT4 in COVID-19 patients was not significantly different from the control group. Patients in the lowest FT3tertile had significantly higher rates of mortality (18/40), mechanical ventilation (24/53.3) and intensive care unit admission (20/44.4). In univariate analysesFT3 remained the most significant independent predictor of death.

1.5. Conclusions

The changes in serum TSH and FT3 levels may be important manifestations of COVID-19 courses.FT3 levels can serve as a prognostic tool for disease severity in early presentation of COVID-19.

2. Introduction

It has been recognized that the main target organs attacked by SARS-CoV-2 are lungs, immune system and thyroid gland. Whether thyroid hormones can independently predict mortality in ICU patients remains a matter of debate. Laboratory markers, including D-dimer, ferritin, and lymphocyte count, have additional prognostic value [1]. Prevalence (up to 64%) of sick euthyroid syndrome (SES) among patients with COVID-19, some exhibiting profound decrease in thyroid hormone levels but prognostic significanceis currently unknown [2] FT3correlation with disease seve-

rity and its prognostic value has been shown to be an independent and powerful robust predictor of ICU mortality, [3]. The course of SES includes decline in serum T3 as early as 24 hours after disease onset, accompanied by a reciprocal increase in reverse T3 (RT3). Serum thyroxine levels decline as the acute illness progresses [4] whereas FT4 levels remain normal [5] the recovery phase is characterized by a gradual increase in serum TSH level [4] and may even be prolonged for months following clinical recovery. Of all the thyroid hormones, FT3 stands out as a marker of SES because it is the most dynamic hormone in the evolution of SES and is conventionally measurable, as opposed to RT3 [6].

3. The Aim

Owing to lack of thyroid dysfunction data in critically ill covid -19 Egyptian patients, we conducted this study to prognostically evaluate whether they can be used as a predictor of patients outcome at COVID-19 presentation.

4. Subject and Method

Our study involving 60 healthy control of similar age and sex and a total of 180 adult patients, 60 non covid pneumonia patients with similar degree of severity included as another control group to find any unique effects of COVID-19 on thyroid function, 120 positive covid-19 divided according clinical classifications into: moderate, severe, and critical, Critical admitted to ICU and classified as survivors and non survivors. The patients were based on the outcome of treatment. On admission (TSH, FT3 and FT4) besides other relevant investigations. Thyroid hormones were assayed using chemiluminescence immunoassay. Quantitative enzyme-linked immunosorbent (ELISA) used for IL-6 assay. APACHE-II score was calculated. Excluded from this study patients with thyroid disease history, patients taking drugs altering thyroid functions, pregnant or those who were pregnant in the past 6 months, taking amiodarone or any hormonal therapy except insulin. Study approved by hospital ethics committee and written consent was obtained from patients or their legal guardians.

5. Statistics

Statistical analysis was performed using software SPSS version 17. Data are presented in the form of mean value ± standard deviation for continuous variables and percentage for categorical variables. Baseline characteristics between groups were compared using unpaired Student's t-test for continuous variables and Fisher's exact test for categorical variables. Variables were compared among FT3 tertiles and between the groups of survivors and nonsurvivors. Receiver-operating curve (ROC) analysis enabled evaluation of FT3 predictive ability to mortality; the best cutoff point was determined using the Youden index. Univariate logistic regression analyses were further performed to assess ICU mortality association with each of the mortality predictors. $P< 0.05$ was considered statistically significant.

6. Results

Abnormal low thyroid function parameters were found in 60.8 % (73/120) of COVID-19 patients. Serums TSH, FT4and FT3 levels were significantly lower in COVID-19 patients than healthy control group and non COVID-19 pneumonia patients. Also, IL-6 was significantly higher in COVID-19 patients than healthy control group and non COVID-19 pneumonia patients, so IL-6 with thyroid function considered risk factors for COVID-19 (Table1). The degree of decrease of TSH and FT3 was positively correlated with disease severity. The more severe the COVID-19 infection was, the lower the TSH and FT3 levels, with statistically significant differences ($p<0.001$) (Table 2). A full comparison of survivors with non survivors is presented in (Table 3), there were no significant differences regarding mean room air saturation. White blood cell (WBC), absolute neutrophil count, CRP, Urea and albumin were significantly different between non-survivors and survivors. Several markers for severe disease, including creatinine, LDH and D-dimer, were borderline significant between the 2 groups. Patients who died were significantly older and had a higher APACHE-II score. These patients had FT3 level significantly lower than that of the survivors. Covid patients were divided in (Table 4) into tertiles according to their FT3 levels (2.4-4.0, 4.1-4.8, and 4.9-7.4 pmol/L, respectively). Patients in the lowest tertile included patients with FT3 value below or in the lower part of the reference range; this group of patients included those with SES. Demographic and clinical characteristics were compared between the FT3 tertiles. Participants in the lowest FT3 tertile were significantly older compared with the higher tertiles, had a higher APACHE-II score and a higher prevalence of diabetes mellitus and hypertension. No significant differences were found with respect to sex, but had significantly lower mean room air oxygen saturation. Also, had higher creatinine and CRP level, lower mean lymphocyte count, albuminandFT3 but no significant differences between the groups in TSH or FT4 level. Other laboratory markers for severe disease were also significantly different between tertiles including LDH, ferritin and D-dimer. There was 23 deaths, of which 18 were in the lowest tertile of FT3. Regarding Outcomes**,** The average length of hospitalization was not significantly different between the groups. Patients in the lowest FT3 tertile had a significantly higher mortality rate, more mechanical ventilation and ICU hospitalization. An ROC curve for the association between FT3 levels and death is shown in (Table 5). With a cutoff value of 4.0pmol/L, area under the curve (AUC) was 0.283, the sensitivity was 0.375and the specificity was 0.786. When compared with other variables that were found to be significantly associated with death, FT3 was superior to age and WBC count AUC (0.79 and0.83, respectively) and inferior to albumin levels and APACHE II score (AUC0.89 and 0.86, respectively) In a univariate analysis, older age, lower FT3 levels and higher APACHE-II, low albumin, low WBC and

neutrophil count were significantly associated with a higher risk of death but neither TSH nor FT4 levels were significant for mortality. The ORs for FT3 and albumin were low because, unlike other variables associated with death, as higher FT3 and albumin levels are associated with a decreased risk of death **(**Table 6**).** Further, we conducted a multivariate logistic regression analysis to determine the independent predictors of ICU mortality Combined values of fT3 and APACHE II was found to have higher probability of predicting mortality (Cox and Snell R2 = 0.652, Nagelkerke R2 = 0.924) than with APACHE II alone (Cox and Snell R2 = 0.286, Nagelkerke R2 = 0.405.

Table1: Demographicand Clinical Data in Covid-19, Non Covid-19 and Healthy Control.

mean (SD)	COVID-19 (n = 120)	Non-COVID-19 (n =60)	Healthy control (n = 60)	P -value
Age	51 ± 18.30	58.79 ± 12.44	54.17 ± 16.51	0.68
Male (%)	31±64.6%	15± 53.6%	51±36.2%	0.34
D-dimer (ng/mL)	7210 ±5124	70 ±17	43±19	0.001*
Ferritin (ng/mL)	1500 ±298	672 ±156	193±11	0.003*
LDH (IU/L)	378 ± 259	137 ±107	141±96	0.023*
ESR	69.7± 19.07	25.1± 15.2	4.21 ± 2.4	<0.001*
CRP (mg/L)	99.43±57.05	28.09± 15.13	4.1±2.6	<0.001*
Alb (g/L)	38.15 ± 3.57	38.70 ± 3.36	47.15 ± 5.1	<0.001*
TSH (mIU/L)	0.90 ± 0.75	1.38 ± 0.68	1.77 ± 1.03	<0.01*
FT4 (pmol/L)	13.23 ± 2.7	15.71 ± 3.4	16.11 ± 2.1	<0.001*
FT3 (pmol/L)	2.46± 2.7	4.72± 1.7	5.10± 1.1	<0.01*
IL6 (pg/mL)	96.10 ± 52.35	7.91 ± 3.99	6.18 ± 1.58	<0.01*
Procalcitonin (mcg/L)	0.41 ± 0.39	0.08 ± 0.16	0.03 ± 0.07	<0.01*
Severity of pneumonia				
Moderate	58(48.3%)	17(28.3%)	-	0.11
Severe	21(17.5%)	21(35.0%)	-	0.07
Critical	41(34.2%)	22(36.7%)	-	0.79

Table 2: Comparison of COVID-19 Subgroups According Clinical Severity.

	Covid			
	Moderate (n=58)	**Severe (n=21)**	**Critical (n=41)**	**p-value**
TSH	1.02 [0.37-1.49]	0.69 [0.21-0.87]	0.21 [0.075 -0.36]	<0.001*
FT4	13.23(12.72-17.16)	14.23(13.12-16.29)	12.93(12.12-15.96)	0.113
FT3	4.23 (3.4-5.4)	3.37 (3.0-4.2)	2.43 (2.11-3.8)	0.001*
Alb	43.40 [37.90- 44.90]	38.20 [35.60- 41.40]	34.40 [32.05- 37.45]	<0.001*

*The p-value means that there is difference as compared among all the groups.

Table 3: Comparison of Survivors to Non Survivors in Critical Cases.

	Critical		P value
	Survivors (n = 33)	**Non Survivors (n = 8)**	
Age, mean (SD)	52.09 (17.13)	71.13 (16.76)	0.003*
DM (%)	12 (36.3)	3 (37.5)	0.712
HTN (%)	11 (33.3)	6 (75.0)	0.031*
APACHE score	16.54±6.23	29.00±11.55	<0.001*
Oxygen saturation (%)	86.48±15.20	83.90 ± 14.16	0.39
HR (bpm)	89.65 ±16.48	94.90 ±25.71	0.43
WBC (K/mL)	6.98±3.34	13.96 ±7.63	0.001*
Neutrophils (K/mL)	5.34±2.90	11.56 ± 8.21	0.001*
Lymphocytes (K/mL)	1.01±0.60	0.79±0.35	0.27
Serum urea (mg/dl)	57.87±29.74	107.82±55.81	<0.001*
Cr (mg/dL)	0.85±0.39	1.37±0.89	0.05*
Albumin (g/dL)	3.89±0.51	2.87±0.48	<.001*
CRP (mg/L)	79.14±78.89	151.80±88.5	0.045*
D-dimer (ng/mL)	4780± 9521	13174±16624	0.05*
Ferritin (ng/mL)	656 ±658	561±478	087
LDH (IU/L)	391±152	469 ±207	0.04*
TSH (mIU/L)	0.71± 0.65	0.15±0.68	0.49
FT4 (pmol/L)	12.92± 5.81)	12.39 ± (3.81	0.48
FT3 (pmol/L)	4.12±0.89	2.61±0.64	<.001*

Table 4: Patients Divided into FT3 Tertiles.

	FT3 tertiles			P value
	2.4-4.0 pmol/L =45	4.1-4.8 pmol/L =37	4.9-7.4 pmol/L =38	
Age	65.25 ±14.46	54.57±15.13	44.62±19.43	0.007*
Male	74.0±16	75.9±14	52.9±10	0.252
Female	26.0±5	24.4 ±4	46.7±9	0.212
DM (%)	25 (55.0)	9 (24.3)	6 (15.8)	0.033*
HTN (%)	22 (48.8)	17 (45.9)	7 (18.4)	0.039*
APACHE score	6.10±3.56	3.27±1.47	2.15 ± 1.94	<.001*
Oxygen saturation (%)	83.05±15.79	90.98±5.41	92.61±6.01	0.008*
HR (bpm)	92.62± 19.32	77.58±14.40	99.97±15.57	0.006*
WBC (K/mL)	12.67±6.28	8.06± 2.56	7.65±2.67	0.26
Neutrophils (K/mL)	8.99 ±7.28	5.12±2.41	5.46± 2.5	0.18
Lymphocytes (K/mL)	0.88 ± 0.46	1.09± 0.61	1.41 ±0.57	0.004*
Cr (mg/dL)	1.37±0.81	1.01± 0.36	0.57 ±0.15	.001*
Albumin (g/dL)	3.19±0.59	3.71±0.63	3.79 ±0.62	0.027*
CRP (mg/L)	154.68 ±90.48	80.70 ±77.51	31.26 ±60.73	<.001*
D-dimer (ng/mL)	8011±14410	1922±2552	6697 ±18253	0.009*
Ferritin (ng/mL)	899±691	597 ±396	189±250	0 .003*
LDH (IU/L)	501±231	317±131	276±8	0.016*
TSH (mIU/L)	0.47±0.51	0.89±0.29	1.19±0.53	0.27
FT4 (pmol/L)	12.68±4.68	12.85±3.47	13.97±3.45	0.62
FT3 (pmol/L)	3.47±(0.41	4.52±0.31	5.49±0.59	<.001*
LOS in days, mean (SD)	38.96 ±32.71	20.67± 21.43	11.68±10.21	0.11
Death (n, %)	18 (40.0)	3 (8.1)	2 (5.2)	0.007*
ICU (n, %)	24 (53.3)	10 (27.0)	2(5.2)	0.005*
Mechanical ventilation (n, %)	20 (44.4)	11 (29.7)	0 (0.0)	0.006*

Table 5: Sensitivity and specificity in predicting COVID-19.

Test	Area under the curve	Sensitivity	Specificity	P-value
IL6	0.939	0.967	0.361	<0.01*
TSH	0.365	0.429	0.667	0.06
FT3	0.283	0.375	0.786	<0.01*
FT4	0.542	0.468	0.384	0.49
Age	0.79	----	----	----
WBCs	0.83	----	----	----
Albumin	0.89	----	----	----
APACH- II	0.86	----	----	----

Table 6: Univariate analysis Regression Analyses.

	OR / CI	P value
Age, mean (SD)	1.07 (1.02-1.12)	0.007*
DM (%)	3.0 (3.12-17.25)	0.023*
HTN (%)	5.0 (1.12-22.27)	0.035*
APACHE score	1.7 (1.22- 2.37)	0.0017*
WBC (K/mL)	1.34 (1.11- 1.63)	0.0026*
Neutrophils (K/mL)	1.37 (1.12-1.67)	0.0024*
Lymphocytes (K/mL)	0.39 (0.09-1.7)	0.21
Cr (mg/dL)	3.28 (1.09- 9.84)	0.034*
Albumin (g/dL)	0.02 (0.00 -0.25)	0.003*
CRP (mg/L)	1.01 (0.99-1.01)	0.07
D-dimer (ng/mL)	1.0 (0.99-1.00)	0.23
Ferritin (ng/mL)	0.99 (0.99-1.00)	0.71
LDH (IU/L)	1.0 (0.00-1.01)	0.07
TSH (mIU/L)	1.07 (0.87-1.31)	0.51
FT4 (pmol/L)	1.02 (0.87-1.21)	0.8
FT3 (pmol/L)	0.17 (0.05, 0.54)	0.003*
IL-6	1.83 (59.83–140)	0.00*

7. Discussion

Classification of COVID-19 patients admitted to our hospital was higher than moderate. Clinical observations have revealed a relatively high prevalence of SES among patients with COVID-19, [4]. These observations have raised the question of whether FT3 levels represent an integrative indicator of disease severity and a patient's reserve early in the course of COVID-19 disease. Previous studies conducted to demonstrate any association between thyroid hormone levels and prognosis in critically ill patient's yielded inconsistent results. Some could not establish an association between fT3 and adverse outcomes [7] in agree with one study, we found no significant difference in TSH andFT4 level between survivors and

deceased patients; however, the deceased patients had significantly lower FT3 levels as compared to survivors [8]. The most typical alterations in euthyroid sick syndrome are decreased T3, low or normal T4, and normal or slightly decreased TSH level [9.10] SARS is a severe infectious illness that has extensive effects on multiple organ systems. A previous study reported that extensive injury to thyroid follicular epithelial and para-follicular cells or changes in TSH-secreting cells in the pituitary [7,11] Another study showed that TT3, TT4 and TSH levels of patients with SARS were considerably lower than those of controls in both the progression and recovery phases, [8] SARS-CoV-2 is similar in structure and pathogenicity with SARS-CoV. Thus, we suspected that SARS-CoV-2 also might affect TSH-secreting cells. We also found low TSH and FT3 levels in COVID-19 patients and the degree of decrease positively correlated with COVID-19 severity. Our findings are in agree with study from China, which found lower TSH levels in more severely affected patients of COVID-19 and in contrast to a study from Italy in which COVID-19 patients were found to have thyrotoxicosis after a confirmatory diagnosis of COVID-19,(2,12) The fact that serums TSH level in COVID-19 patients were significantly lower when compared with non-COVID-19 pneumonia patients with a similar degree of severity which indicates that there might be a unique effect of COVID-19 on TSH-secreting cells. Two possible mechanisms is suggested, One is direct viral effect on pituitary cells and this was contradicted by another study which proposed an indirect effect due various systemic changes such as pro-inflammatory cytokines activation by the virus [9,10] or its treatment led to hormonal changes in the pituitary–endocrine axis feedback loops or chronic stress from hypoxemia. More insights are emerging into immunogenic and hormonal overlap of a novel disease may further complicate COVID-19 management and recovery, as corticosteroids used in severe COVID-19 treatment may cause auto-immune damage to the thyroid gland [13,14] Also, Cytokines particularly IL-6are central mediators of endocrine changes related to systemic illness, with specific effects on the thyroid gland. Course and severity of COVID-19 are closely linked to action of several cytokines and presence of a cytokine storm induced by the virus. Pro-inflammatory cytokines, including IL-6 which interact with thyroid function, as described above, lead to acute respiratory distress syndrome aggravation and widespread tissue damage resulting in multi-organ failure so may affect outcome [15-16].

One study in agree of our result found that T3 level is inversely proportional to IL-6 with a modest decrease of TSH [13,17] the rise in inflammatory cytokines occurs before the clinical deterioration in patients with COVID-19. Thus, suppression of FT3 may serve as simple indicator of clinically significant increase in cytokines. Moreover, the rise in cortisol in the setting of acute infection may also exert a suppressive effect on TSH secretion, FT4 to FT3 conversion, and an increase in the conversion of FT4 to RT3. Low FT3 is likely to be an integrative marker for host response to COVID-19 infection. Inhibition of the 5'-deiodinaseenzyme is a possible mechanism [18] With respect to critical illness; cytokines (tumor necrosis factor, interferon-alpha, and interleukin) are the most important mediator of this enzyme inhibition. Low T3 levels might reflect a collective measure of pathological processes occurring during critical illness, such as DM and inflammatory status [18]. In agree with some studies, Patients in lowest FT3tertilehad markedly higher disease severity and increased mortality compared with patients in higher tertiles. Low FT3 at presentation remained the main predictor of mortality and prolonged mechanical ventilation time from all variables, suggesting that intensive treatment measures should be taken to reduce the risk of death for the patients with lower FT3 level. The deteriorative feedback regulation of pituitary-thyroid axis and the concomitant injuries of other organs may partially explain the mortality, but the patho-physiological mechanism needs further study [8,19,20] In agree with Gutch et al, ROC curve proved that FT3 was an excellent predictor of mortality superior to age and only slightly inferior to albumin levels and APACHE-II. Furthermore, the combination of APACHE-II scores and FT3 values strengthened the ability to predict mortality outcomes [3]. In line with previous studies. Low FT3 was associated with longer hospital stay and increased ICU admission rate [21] the median age of patients who died in the ICU was higher than that of survivors. Studies have shown that advanced age is risk factor for COVID-19 and associated with disease severity and mortality. In a meta-analysis of 24 observational studies, ICU mortality rate was found to be 41.6 % and in retrospective Italian study, ICU patient's mortality rate was 26%.7. In our study, the mortality rate was slightly higher (56.1%) as not all patients in the ICU were included in the study owing to the study protocol [22,23]. Several studies have demonstrated the association of elevated inflammatory markers (CRP, ferritin) and D-dimer with poor prognosis [8] Similar results were obtained in this study; inflammatory markers and D-dimer levels were observed to be higher in critical patients. The CRP levels of patient's who died in the ICU were higher than those of survivors. These results indicate that prompt evaluation of patients with high CRP levels at admission and early initiation of comprehensive treatment can help decrease mortality rate.

8. Limitations

Study population is relatively small and without potential confounders, such as glucocorticoid treatment, which is very common among these patients. Second, presence of undiagnosed thyroid disease before ICU admission cannot be ruled outand other pituitary hormones were not assessed. Third, interference of other drugs with thyroid function (e.g., furosemide, benzodiazepines, barbiturates and dopamine) could not be completelye liminated because it forms an integral part of critically ill patient management. Therefore, excluding the effect of hormonal changes in pituitary–endocrine axis feedback loops was difficult. However, FT3levels are

not much affected by the alterations in TBG levels due to the above causes. Study examinations of rT3 levels, ultrasound inspections of the thyroid and specific antibody tests were not available. Thyroid profile, follow-up was not done Further studies are needed to determine whether thyroxine supplementation is beneficial.

9. Conclusion:

our findings provide solid evidence of the high risk of altered thyroid function after COVID-19 pneumonia. Suggest that FT3 provides a good prognostic value and serve as a valuable classification tool formerly diagnosed patients with COVID-19. Also, FT3 was the strongest predictor of ICU mortality compared to all other parameters. Further, the combination of FT3 level and APACHE-II scores provided higher probability for predicting mortality in ICU patients.

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