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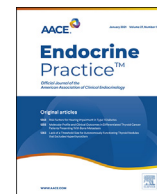
Original Article

Euthyroid Sick Syndrome as a Prognostic Indicator of COVID-19 Pulmonary Involvement, Associated With Poorer Disease Prognosis and Increased Mortality

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A B S T R A C T

Objective: The prevalence of euthyroid sick syndrome (ESS) and its association with the prognosis of COVID-19 and mortality in patients with lung involvement in COVID-19 have not yet been elucidated.
Methods: Clinical and laboratory data of patients with COVID-19 with or without ESS were collected retrospectively and analyzed on admission. All subjects were admitted to the Department of Internal Diseases and Clinical Pharmacology at Bieganski Hospital between December 2020 and April 2021.
Results: In total, 310 medical records of patients with COVID-19 were analyzed retrospectively. Among 215 enrolled patients, 82 cases of ESS were diagnosed. The patients with ESS had higher pro-inflammatory factor levels, longer hospitalizations, and a higher risk of requiring high-flow nasal oxygen therapy or intubation than the patients without ESS. The Kaplan-Meier curve indicated that the patients with ESS had a lower probability of survival when computed tomography showed ≤50% parenchymal involvement compared with that in patients without ESS. However, no differences in mortality were noted in those with more than 50% parenchymal involvement. The survival curve showed that ESS was associated with a higher risk of mortality during hospitalization.
Conclusion: ESS is closely associated with a poor prognosis, including longer hospitalizations, more frequent intubation, transfer to the intensive care unit, and a higher mortality rate in patients with COVID-19. ESS is a potential prognostic predictor of survival, regardless of lung involvement in COVID-19.

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Introduction

In December 2019, the first case of COVID-19, caused by SARS-CoV-2, was reported in China. The virus went on to spread worldwide, which resulted in the World Health Organization (WHO) declaring a pandemic in March 2020.[1] As of September 12, 2021, 223 322 544 cases and 4 625 974 deaths had been reported globally.[2] Observational studies suggest that the poor outcomes in patients with COVID-19 may be partially explained by the changes in thyroid hormone concentrations that are also seen in euthyroid sick syndrome (ESS).[3-6] It is known that ESS is a condition that can develop after an acute illness and can play an important role in predicting the outcome of critically ill patients. In particular, free triiodothyronine (fT3) is believed to have considerable prognostic power regarding ICU mortality.[7,8] Furthermore, changes in thyroid hormone metabolism observed in muscle tissue during severe illnesses may explain the pathogenesis of respiratory failure.[9-11]

ESS is characterized by alterations in thyroid function associated with an acute illness. It is associated with a decrease in serum triiodothyronine (T3) levels with no increase in thyroid-stimulating hormone (TSH) levels; this is believed to be associated with the suppression of peripheral thyroxine (T4) deiodination and reduced binding by plasma thyroid binding protein. Other potential abnormalities include decreased T4 levels and increased serum reverse triiodothyronine (rT3). A complete reversal of abnormalities in the thyroid function tests is typically seen after recovery.[12] It remains

unclear whether thyroid hormone replacement is beneficial for patients with ESS,[13] so no patients with a diagnosed ESS in our study received thyroid therapy.

Therefore, the present study aimed to assess whether the patients hospitalized due to COVID-19 with ESS have a more severe course of the disease, an increased need for oxygen therapy, or greater percent involvement of the lungs, as revealed by computed tomography (CT) scans of the chest; it also examines whether they have a higher chance of intubation, ICU hospitalization, and death. This is the first study to investigate the relationship between lung involvement, defined by the percentage extent of lesions visible on a chest CT, and the intensity of oxygen support in patients with COVID-19 with or without ESS during hospitalization. This is also the first study to propose a multivariate regression model for predicting mortality, intubation, and high-flow nasal oxygen therapy (HFNOT) in response to selected risk factors for severe cases of COVID-19: the presence of ESS and lung involvement (percentage of lung parenchyma affected by the disease) as indicated by the chest CT. Our findings should be valuable for clinicians working with patients with COVID-19 who have ESS.

Materials and Methods

Study Design and Participants

Data, including thyroid function tests, were collected retrospectively from the medical records of 310 patients with COVID-19 (age ≥18 years) hospitalized at the Department of Internal Diseases and Clinical Pharmacology at Bieganski Hospital between December 2020 and April 2021. The patients were diagnosed with COVID-19 on admission, confirmed by the presence of SARS-CoV-2 RNA and antigens in the nasal pharyngeal swab.

In total, 215 patients met the inclusion criteria, which include hospitalization because of COVID 19 and a completed thyroid function test on admission to the hospital.

The following exclusion criteria were applied: pre-existing hypothalamic-pituitary gland dysfunction in medical history; previous thyroid surgery; a history of chemotherapy or radiotherapy in the previous 6 months; alternation of the thyroid gland revealed by chest CT scan and described by a radiologist, including nodular

goiter; current use of thyroid hormone therapy; and no full assessment of thyroid gland function examination on admission. Of the 95 patients who were excluded, the following reasons were ascertained: lack of thyroid function test ($n = 30$), hypothyroidism ($n = 25$), alternation of the thyroid gland revealed by chest CT scan and described by a radiologist ($n = 10$), hyperthyroidism ($n = 7$), nodular goiter ($n = 9$), radioiodine therapy ($n = 2$), thyroidectomy ($n = 6$), multihormonal pituitary insufficiency ($n = 1$), and transfer from another unit ($n = 5$).

To be qualified for the ESS group, a patient had to demonstrate decreased fT3 with normal or low TSH levels.[14] Patients with high TSH with normal free thyroxine (fT4) and fT3 levels were classified as having hypothyroidism and patients with low TSH and normal fT4 and fT3 levels were classified as having hyperthyroidism and were excluded from the analysis.

Table 1 shows the characteristics known to be associated with a higher risk for severe COVID-19 (older age, sex, smoking, and pre-existing medical conditions: malignancy, hypertension, diabetes mellitus, chronic lung disease, chronic kidney disease, chronic liver disease, heart failure, coronary artery disease, stroke, or transient ischemic attack).

Data Collection

Patient age, sex, and the levels of basic inflammatory markers such as C-reactive protein (CRP), interleukin-6 (IL-6), and procalcitonin (PCT) were recorded on admission (between 0 and around 24 hours from admission) and before implementation of COVID-19 therapy (except for oxygen support). Thyroid levels were measured within 24 hours of admission to the hospital, regardless of the time of admission. All patients included in the analysis underwent laboratory testing for thyroid hormones. No data was collected pertaining to the duration of symptoms.

Serum TSH, fT3, and fT4 were measured in a local laboratory (electrochemiluminescent method). The reference ranges were 0.27 to 4.2μU/mL (TSH), 3.1 to 6.8pmol/L (fT3), and 12.0 to 22.0 pmol/L (fT4). CRP, IL-6, and PCT were measured in a local laboratory (CRP—immunoturbidimetric method; IL-6 and PCT—electrochemiluminescent method). High-resolution chest CT scans performed between 0 and 48 hours from admission were also

Table 1
Characteristics of the COVID-19 Patients With ESS and Those Without

Parameter median/ (IQR)	Total patients N = 215	Patients with ESS n = 82	Non-ESS patients n = 133	P value
Sex n, (%)				>.05
female	93 (43.3)	38 (46.3)	55 (41.4)	
n, (%) male	122 (56.7)	44 (53.7)	78 (58.4)	
Age (y)	68 (58; 78)	73 (66.0; 82.3)	65 (52.5; 74.0)	<.001
TSH (μU/mL; normal range 0.27-4.2)	1.1 (0.6; 1.6)	1.07 (0.6; 1.7)	1.10 (0.6; 1.7)	>.05
FT3 (pmol/L; normal range 3.1-6.8)	3.3 (2.6; 4.0)	2.5 (2.2; 2.8)	3.7 (3.4; 4.3)	<.0001
FT4 (pmol/L; normal range 12.0-22.00)	17.1 (14.5; 19.7)	16.4 (13.3; 19.3)	17.8 (15.0; 20.3)	<.05
Medication, n (%)				
remdesivir	47 (21.7)	15 (18.3)	32 (24.1)	>.05
tocilizumab	19 (8.8)	9 (11.0)	10 (7.5)	>.05
Pre-existing Medical Conditions and Risk factors for Severe COVID-19				
Malignancy	17 (7.9)	6 (7.3)	11 (8.3)	>.05
Hypertension	139 (64.7)	55 (67.1)	84 (63.1)	>.05
Diabetes mellitus	60 (27,9)	25 (30.5)	35 (26.3)	>.05
Chronic lung disease	25 (11.6)	12 (14.6)	13 (9.8)	>.05
Chronic kidney disease	20 (9.3)	8 (9.7)	12 (9.0)	>.05
Chronic liver disease	25 (11.6)	7 (8.5)	18 (13.5)	>.05
Heart failure	33 (15.3)	16 (19.5)	17 (12.8)	>.05
Coronary artery disease	45 (20.9)	22 (26.8)	23 (17.3)	>.05
Stroke or transient ischemic attack	14 (6.5)	8 (9.7)	6 (4.5)	>.05
Smoking	27 (12.5)	9 (10.9)	18 (13.5)	>.05
Obesity	49 (22.8)	12 (14.6)	37 (27.8)	<.05

Abbreviations: ESS = euthyroid sick syndrome; fT3 = free triiodothyronine; fT4 = free thyroxine IQR = interquartile range; TSH, thyroid-stimulating hormone.

examined to determine the percentage of lung parenchyma affected by COVID-19 lesions. For more detailed survival analyses, each group (ESS and non-ESS) was classified into 2 subgroups with regard to the percentage of lung involvement by COVID-19 lesions as determined by a visual quantification of CT images: 50% or less involvement and more than 50% involvement. This is known as a risk factor for early death or ICU admission, especially when lung involvement by pneumonia is more than 50%.[15]

Clinical measures also included the use of supplemental oxygen therapy devices during hospitalization, HFNOT and invasive ventilation; length of hospitalization in days; the need for remdesivir or tocilizumab therapy; and mortality. Mortality was defined as the death of the patient in the hospital (non-ICU department or ICU department) and was evaluated by follow-up of patients who continued treatment in the ICU. Patients discharged from the hospital were censored as observations and were not included in the outcome.

Statistical Analysis

Continuous variables not following normal distribution were expressed as median with an interquartile range (IQR) and analyzed using the Mann-Whitney U test. Categorical data were described using frequencies and percentages. The relationship between categorical variables was assessed using the χ^2 test. The association between ESS and end points was determined using a Kaplan-Meier curve with a 95% confidence interval (95% CI).

A logistic regression model was created to evaluate the following potential risk factors to predict the risk of mortality: HFNOT or intubation in cases of severe COVID-19, the presence of ESS, percentage of lung involvement of lesions (by chest CT), age, sex, smoking, and pre-existing medical conditions (malignancy, hypertension, diabetes mellitus, chronic lung disease, chronic kidney disease, chronic liver disease, heart failure, coronary artery disease, stroke, or transient ischemic attack). Receiver operating characteristics (ROC) and area under the curve analysis of mortality were used to evaluate the predictive power of the final model in predicting the need for intubation and HFNOT in response to risk factors for a severe COVID-19. The goodness of fit of the model was tested with the Hosmer-Lemeshow statistic, where a nonsignificant probability value indicates a good fit. P values lower than .05 were considered statistically significant.

Statistical analyses were performed using Statistica version 13 (StatSoft) and with GraphPad Prism version 7.0 software (GraphPad Software Inc). Odds ratios were calculated with the use of a free online calculator: https://www.gigacalculator.com/calculators/odds-ratio-calculator.php.

Results

Baseline Characteristics of Patients with COVID-19

Among the 215 enrolled patients, 122 (56.7%) were men, and 93 (43.3%) were women. The median age was 68 years (IQR, 58-78 years) old. ESS was diagnosed in 82 (38.1%) patients: 44 (53.7%)

men and 38 (46.3%) women. Patients with ESS were older than the ones without ESS: 73 years (IQR, 66.0; 82.3) vs 65 years (IQR, 52.5; 74.0) ($P < .001$). No sex dominance was observed between ESS and non-ESS groups ($P > .05$). We analyzed the outcomes to evaluate their relationship with age and sex. Results are available in Supplementary Materials 1. Remdesivir was used in 47 (21.7%) cases and tocilizumab in 19 (8.8%) (Table 1). Angio-pulmonary CT scan was performed in 34 (15.8%) patients and pulmonary embolism was confirmed in 10 (4.7%). The risk factors for severe COVID-19 observed in the patients are presented in Table 1. The most significant risk factors are hypertension, present in 139 patients (64.7%); diabetes in 60 patients (27.9%); coronary artery disease in 45 patients (20.9%); heart failure in 23 patients (10.7%); history of stroke or transient ischemic attack in 14 patients (6.5%); history of or current malignancy in 17 patients (7.9%); and pulmonary diseases (asthma, chronic obstructive pulmonary disease (COPD), overlap asthma-COPD syndrome) in 25 patients (11.6%).

For further analyses, the patients with COVID-19 were divided into group 1 comprising those with ESS ($n = 82$) and group 2 without ESS ($n = 133$).

For more detailed survival analyses, each group was classified into 2 subgroups with regard to the percentage of lung involvement by COVID-19 lesions: 50% or less involvement and more than 50% involvement.

Data regarding the fT3, fT4, TSH levels, and treatment of the studied groups are given in Table 1.

Laboratory Findings on Admission

The laboratory results of all included patients with COVID-19, with or without ESS on admission, are presented in Table 2. The results indicate that those with ESS had higher levels of inflammatory markers, including (CRP and PCT). Slightly higher IL-6 levels were observed among the patients with ESS; however, this difference was not significant ($P = .08$).

ESS is Associated with a Higher Need for HFNOT and Invasive Ventilation in COVID-19 Patients

The number of patients requiring HFNOT for ESS was 7 out of 82 (8.5%) vs 3 out of 133 (2.3%) for non-ESS ($P < .05$). The number of patients intubated and transferred to the ICU for ESS was 15 out of 82 (18.3%) vs 8 out of 133 (6.0%) for non-ESS ($P < .01$). The odds ratio with 95% CI and P values for HFNOT and intubation for patients without ESS and patients with ESS are given in Figure 1.

A logistic regression model was generated to evaluate the potential risk factors for severe COVID-19, ie, ESS, percentage of lung involvement identified on chest CT, older age, sex, smoking, and pre-existing medical conditions (malignancy, hypertension, diabetes mellitus, chronic lung disease, chronic kidney disease, chronic liver disease, heart failure, coronary artery disease, stroke, or transient ischemic attack) to predict the risk of HFNOT or intubation. The final model is presented in Table 3. The presence of ESS and more than 50% lung involvement by COVID-19 lesions predisposes the patient to an increased chance of intubation. However, only more than 50%

Table 2
Laboratory Findings of COVID-19 Patients at Admission

Parameter median/(IQR)	Total patients N = 215	Patients with ESS n = 82	Non-ESS patients n = 133	P value
CRP (mg/L; normal range <5.0)	71.4 (26.8; 124.1)	79.3 (39.1; 142.5)	61.5 (22.0; 111.8)	<.05
PCT (ng/L; normal range <0.5)	0.12 (0.1; 0.3)	0.15 (0.07; 0.2)	0.11 (0.1; 0.6)	<.0001
IL-6 (ng/mL; normal range <7.0)	43.10 (21.1; 87.3)	51.0 (19.8; 85.9)	36.4 (24.9; 94.5)	>.05

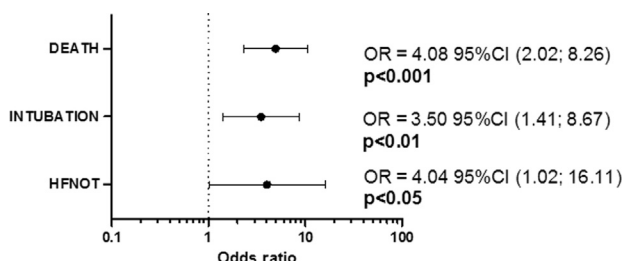Abbreviations: CRP = C-reactive protein; ESS = euthyroid sick syndrome; IL-6, interleukin-6; IQR = interquartile range; PCT = procalcitonin.

Fig. 1. Odds ratio (OR) for patients with ESS and patients without euthyroid sick syndrome (ESS) for death, intubation, and high-flow nasal oxygen therapy (HFNOT).

involvement by COVID-19 lesions was associated with a higher need for oxygen therapy in patients with COVID-19.

The Hosmer-Lemeshow test for goodness of fit indicated good calibration for the model (respectively for HFNOT, $P = .999$, and intubation, $P = .743$). An ROC analysis for the model (Fig. 2) yielded areas under the curve of 0.954 and 0.914 (95% CI: 0.916-0.992 and 0.856-0.973), respectively, for HFNOT and intubation.

ESS is Associated with a Higher Risk of Mortality in Patients with COVID-19

Of the 215 patients, 41 (19.1%) died. Patients with ESS had a significantly higher mortality rate during hospitalization than those without, 28 out of 82 (34.1%) for those with ESS vs 15 out of 133 (11.3%) for those without ($P < .0001$). The OR with 95% CI and P values regarding mortality for both groups are given in Figure 1. The Kaplan-Meier survival curves are shown in Figure 3 B. Additionally, patients with ESS were more likely to stay in the hospital than those without. The median length of hospitalization was 10.5 days [95% CI (7; 12)] for the ESS group vs 9.5 days [95% CI (8; 11)] for the non-ESS group ($P < .05$; Fig. 3 A).

A logistic regression model was generated to identify the selected risk factors for severe COVID-19 and predict the risk of mortality. The final model is presented in Table 3. ESS, the percentage of lung involvement identified on chest CT, and diabetes mellitus increase mortality in patients with COVID-19. The Hosmer-Lemeshow test for goodness of fit indicated that the model was well calibrated ($P = .793$). An ROC analysis for the model (Fig. 2) yielded an area under the curve of 0.888 (95% CI, 0.837-0.938).

Radiological Findings on Admission

Each patient underwent a chest CT scan, where the percentage of inflammatory changes due to COVID-19 was assessed. The CT scans were performed in the same roentgenologic laboratory, processed by the same team of technicians in radiology, and interpreted by the same 2 radiologists, each having a specialization. All doubts were discussed and resolved by the same team. Imaging examinations showed that most patients (197 out of 215; 91.6%) had inflammatory lesions. Patients with ESS (78 out of 82, 95.1%) were more likely than patients without ESS (119 out of 133, 89.5%) to develop characteristic lesions in lung parenchyma associated with COVID-19 as confirmed by a chest CT scan ($P < .05$; Fig. 4 A). The Kaplan-Meier curves indicate a lower survival probability in patients with COVID-19 with ESS when the chest CT findings at admission were 50% or less; no significant differences in survival were observed between the ESS and non-ESS groups regarding lung involvement of >50% ($P = .19333$) (Fig. 4 B and C).

Discussion

There is an urgent need to identify patients with COVID-19 who are at a higher risk of a severe course of the disease. Currently, the risk factors for COVID-19 include older age, male sex, and pre-existing medical conditions.[16-18] The European Centre for Disease Prevention and Control outlines health conditions reported among adult patients with severe COVID-19 disease: diabetes,[18-20] obesity,[21] hypertension,[18,22,23] history of heart failure,[22] solid organ tumors,[24] ischemic heart disease,[17,23,25] chronic respiratory disease,[18,26] cancer,[25,27] pregnancy,[28,29] neurologic conditions,[22,25,26,30] COPD,[22,23] smoking,[22,23,31] and chronic kidney disease.[24-26]

However, while researchers have reported an association between thyroid dysfunction (TD) and COVID-19 severity,[14,32] as well as increased mortality among patients with TD and COVID-19,[33] ESS was not mentioned in the most recent data update from the European Center for Disease Prevention and Control (26 April 2021)[16] as a factor that can aggravate the course of COVID-19. The present retrospective study was performed to confirm whether ESS can be used to predict the severity of COVID-19. Out of the 310 patients hospitalized due to COVID-19 who agreed to join the study, 215 met the inclusion criteria. The patients were divided into 2 groups based on fT3 levels: an ESS group, (defined as decreased fT3 levels; $n = 82$), and a non-ESS group, (defined as normal fT3 levels;

Table 3

Multivariate Regression Model for Predicting Mortality, Intubation, and HFNOT in Response to Selected Risk Factors for Severe COVID-19

Mortality			
	OR	95% CI	P value
ESS	3.163	1.276 to 8.225	<.05
ESS when 50% or less lung involvement identified on chest CT	3.870	1, 091 to 11.19	<.05
Percentage lung involvement identified on chest CT (0%-100%)	1.052	1.033 to 1.074	<.0001
Diabetes mellitus	3.35	1.325 to 8.859	<.05
Intubation			
ESS	4, 155	1.145 to 17.54	<.05
ESS when 50% or less lung involvement identified on chest CT	4.421	1, 158 to 18.23	<.05
Percentage lung involvement identified on chest CT (0%-100%)	4.256	0.9178 to 0.9678	<.0001
HFNOT			
Percentage lung involvement identified on chest CT (0%-100%)	1.099	1.408 to 1.480	<.001

Abbreviations: CI = confidence interval; CT = computed tomography; ESS = euthyroid sick syndrome; HFNOT, high-flow nasal oxygen therapy; OR = odds ratio.
Factors included are ESS, percentage lung involvement identified on chest CT (0%-100%; 0%-50%, and more than 50%), older age, sex, smoking, and pre-existing medical conditions: malignancy, hypertension, diabetes mellitus, chronic lung disease, chronic kidney disease, chronic liver disease, heart failure, coronary artery disease, stroke, or transient ischemic attack in patients with COVID-19.
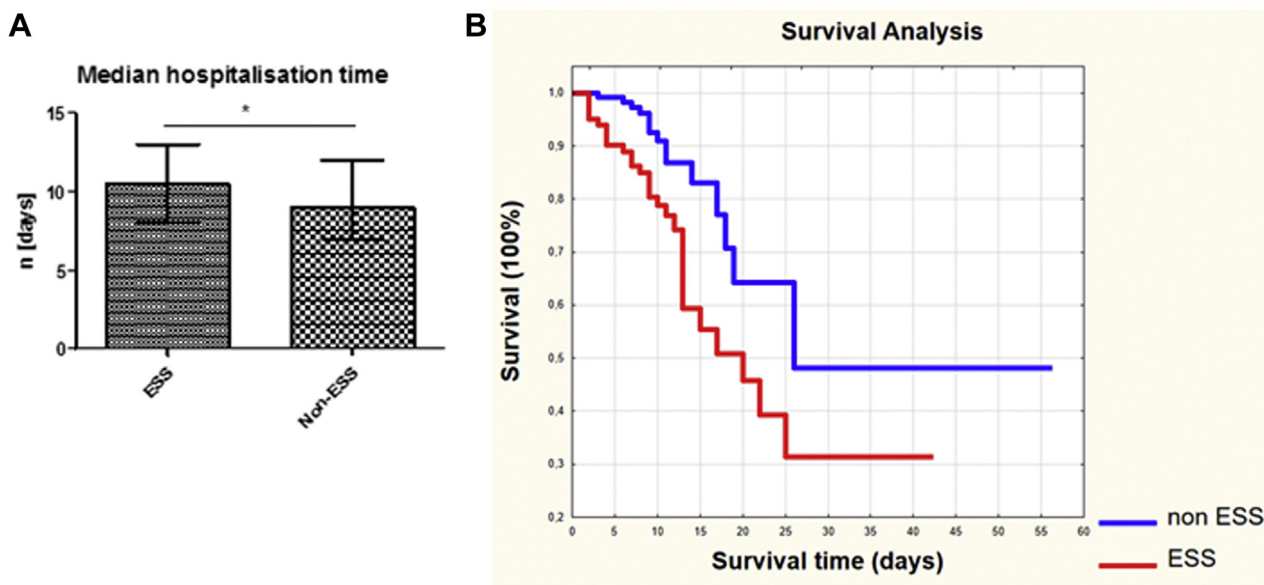Only statistically significant data is included in the table.

Fig. 2. ROC curve analysis for the: *A,* mortality, and *B,* intubation. *C,* high-flow nasal oxygen therapy (HFNOT) model in predicting response to the risk factors for severe COVID-19 include ESS, percentage lung involvement identified on chest CT, older age, sex, smoking, and pre-existing medical conditions in patients with COVID-19. *CT* = computed tomography; *ROC* = receiver operating characteristics.

$n = 133$). The fact that the group of patients with ESS was relatively large is an additional advantage for our work, as most previous reports have based their findings on a smaller number of patients with ESS ([$n = 41$],[14] [$n = 27$],[6] [$n = 12$],[33]) or TD ([$n = 32$],[32] [$n = 25$][33]), subnormal TSH ($n = 11$), or low fT3 ($n = 12$).[34]

The frequency of ESS in the group of patients diagnosed with COVID-19 admitted to our department was 38%. The frequency of ESS in patients diagnosed with COVID-19 in the literature oscillates between 6%[32] and 27.52%.[14] The difference in the prevalence of ESS may be explained by the distinctions between the examined populations, eg, the median age of our cohort was 68 years vs median ages of 47 years[14] and 54 years[6,33] in the cohorts of published articles. Moreover, a prevalence of comorbidities differentiates the discussed populations. Whereas our cohort had 64.7%, 27.9%, and 20.9% patients with hypertension, diabetes, and cardiovascular disease, respectively, the population analyzed by Zhang et al[33] had 28.2%, 18.3%, and 12.7% and Zou et al[14] had 11.41%, 6.71%, and 4.7% of patients with hypertension, diabetes, cardiovascular disease, respectively.

The 2 groups were compared with regard to selected parameters associated with the COVID-19 course, use of HFNOT or intubation, ICU hospitalization, and death. For more detailed survival analysis, each group was subdivided according to the percentage of lung involvement by COVID-19 lesions: 50% or less and more than 50%.

Visual quantification of the CT lung lesions is a known risk factor for early death or ICU admission, especially when lung involvement is more than 50%.[15] The present study is the first to compare patients with ESS and those without ESS with regard to lung involvement with lesions according to CT imaging. While the changes in the levels of most thyroid hormones can be used to predict the outcome of critically ill patients, fT3 has the greatest power to predict ICU mortality.[8] Lower fT3 levels have been found to be associated with greater mortality among ICU patients with acute respiratory distress syndrome .[7] Furthermore, thyroid hormones are known to influence muscle strength,[11] and reversible respiratory muscle weakness with diaphragmatic dysfunction has been identified in the course of hypothyroidism.[9]

However, the prevalence of ESS and its association with the prognosis of COVID-19 remains unclear. Previous studies have reported that TD is closely associated with a higher mortality rate in patients with COVID-19. Zhang et al[33] reported that patients with TD had a significantly higher mortality rate than those without TD during hospitalization (20% vs 0%; $P = .002$). Similarly, Lang et al[35] found low fT3 levels to be associated with an increased risk of in-hospital death after adjusting for confounding factors (hazard ratio, 13.288; 95% CI, 1.089-162.11; $P < .05$).

Our current findings show that patients with ESS had a significantly higher mortality rate during hospitalization, ie, 28 out of 82 (34.1%), than those without ESS, ie, 15 out of 133 (11.3%) ($P < .0001$). Similarly, Schwarz et al[5] reported a mortality rate of 40% among patients with both COVID-19 and ESS. In addition, a low fT3 level may be a potential prognostic predictor of all-cause mortality in severe cases of COVID-19.[36] A generated logistic regression model revealed that ESS is a powerful predictor of COVID-19 mortality in hospitalized patients. The cost-effectiveness of recommending a thyroid panel to predict COVID 19 severity needs to be calculated.

Additionally, our data indicate that patients with ESS had a longer length of hospital stay than those without ESS. The median time of hospital treatment was 10.5 days (95% CI; 7, 12) for the ESS group vs 9.5 days for the non-ESS group ($P < .05$). Patients with COVID-19 and TD have been found to be more likely to stay in a hospital for more than 28 days than those without TD.[33] However, no such difference was found in a similar study.[5,14]

Our study is the first to demonstrate an association between ESS and mortality in patients with 50% or less lung involvement in COVID-19. The Kaplan-Meier curves indicated a lower survival probability in patients with COVID-19 and ESS when the chest CT findings at admission were 50% or less; no significant differences were observed at an involvement of >50% ($P = .19333$). In addition, a significantly higher number of patients with ESS were intubated and transferred to the ICU than patients without ESS. This suggests that ESS is a potential prognostic predictor, regardless of the lung involvement in COVID-19. Previous studies have also noted that ESS may be an independent predictor of clinical deterioration in patients with mild to moderately severe COVID-19.[6]
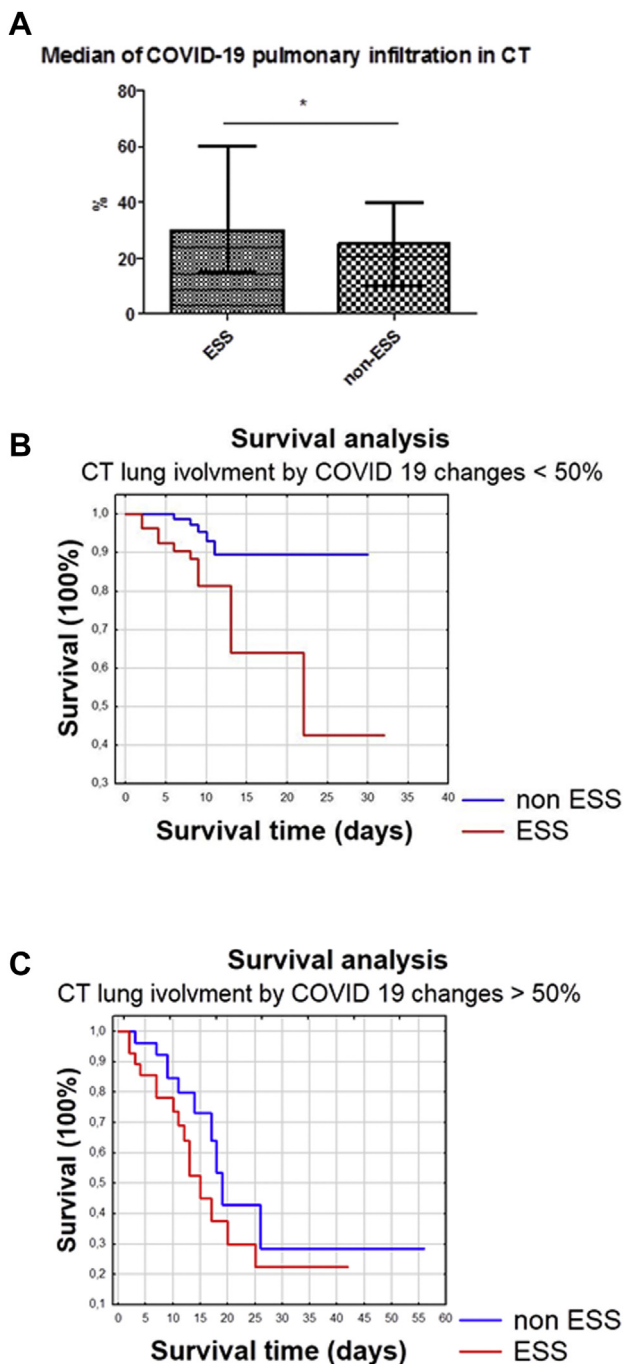
A

Median of COVID-19 pulmonary infiltration in CT

B

Survival analysis
CT lung ivolvment by COVID 19 changes < 50%

C

Survival analysis
CT lung ivolvment by COVID 19 changes > 50%

Fig. 3. *A,* Hospitalization time in patients with euthyroid sick syndrome (ESS) vs patients without ESS: median 10.5 days, interquartile range(IQR, 8, 13) for ESS vs 9.0 days IQR (7, 12) for non-ESS (*P* < .05). *B,* Kaplan-Meier curve for mortality in patients with COVID-19 with ESS vs patients without ESS (*P* = .00281).

This is the first study to investigate the relationship between a greater need for HFNOT, invasive ventilation during hospitalization, and lung involvement, as identified by a chest CT (%), in patients with COVID-19 with or without ESS. Patients with ESS demonstrated a significantly higher risk of needing HFNOT and invasive ventilation. Unexpectedly, we also observed a lower median percent involvement of lung lesions on the chest CT scans in the ESS group than in the non-ESS group when analyzed with regard to the need for mechanical ventilation. This can be partially explained by the influence of thyroid hormones on muscle function.[7] While the

effects were not statistically significant, there is clearly a noticeable tendency that requires research on a larger group of patients.

In addition, a logistic regression model was used to evaluate the predictive potential of selected risk factors for severe COVID-19 for the risk of mortality, HFNOT, and intubation. The analysis confirmed our previously presented results. ESS and percentage of lung parenchyma involvement in COVID-19 can predict an increased risk of mortality and intubation in patients with COVID-19. The analysis also found diabetes to be a predisposing factor for increased mortality for both patients with ESS and those without ESS. No significant differences in the incidence of diabetes were found between the 2 groups. Whereas, only the percentage of lung involvement identified on a chest CT is a factor that can predict a higher need for oxygen therapy in patients with COVID-19. However, the Kaplan-Meier curve indicated that the patients with ESS had a lower probability of survival than those without ESS at <50% of lung involvement identified on chest CT. No differences in mortality were observed when comparing those with >50% parenchymal involvement.

Our findings also indicate that patients with COVID-19 and ESS tended to present with persistently higher inflammatory biomarkers (CRP and PCT). However, it should be noted that the level of PCT in both patients with ESS and those without ESS was within normal ranges in our study. This further indicates that ESS might be closely associated with a more severe inflammatory response. The results of our research on inflammatory biomarkers are consistent with the previous reports conducted by Zhang et al[33] and Zou et al.[14] It has been shown that patients with severe COVID-19 infection may undergo a cytokine storm characterized by hyperactivity of the Th1/Th17 immune response, with increased production of several pro-inflammatory cytokines, including IL-6, interleukin 1 B, and tumor necrosis factor α .[37] In the present study, no significant difference in IL-6 levels was found between patients with ESS and those without ESS. However, a slight increase was observed in patients with ESS (36; 24.9, 94.5) vs (51; 19.8, 85.9) in patients without ESS (*P* = .08). In summary, ESS is a common factor, and this fact should be taken into account when performing thyroid function tests on patients with COVID-19. Knowledge about the pathophysiology and course of ESS should be established among clinicians involved in the treatment of patients with a SARS-CoV-2 infection. Thyroid hormones are known to influence muscle strength,[8] and reversible respiratory muscle weakness with diaphragmatic dysfunction has been identified in the course of hypothyroidism.[13,14] A list of well-known and established risk factors for a serious course of COVID-19[16] exists, but an awareness of the potential impact of ESS on the course of COVID-19 may help in organizing patients to specific departments upon hospitalization (eg, departments with access to HFNOT).

Limitations

This study has several limitations. Firstly, the patients were transferred to the hospital at different times from the onset of illness. Secondly, it remains unclear whether the presence of ESS and age are independent risk factors for death in patients with COVID-19 or whether a correlation exists between the 2 variables.

Conclusion

ESS appears to be closely associated with a poorer prognosis, including longer hospitalization, a higher frequency of intubation, transfer to the ICU, and a higher mortality rate. The fact that the ESS group demonstrated higher mortality even when the chest CT findings at admission were 50% or less suggests that ESS is a potential prognostic predictor, regardless of the lung involvement due
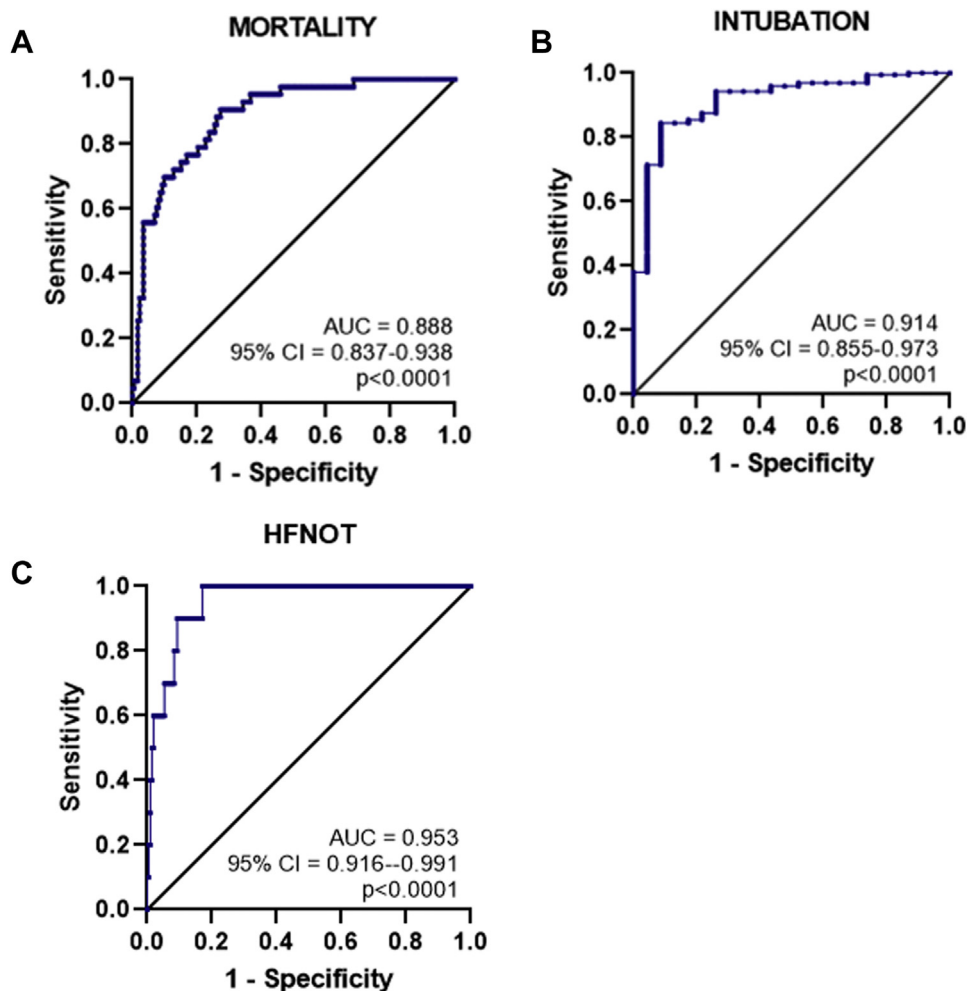
Fig. 4. *A,* Median lung inflammatory infiltration in patients with COVID-19: 30% interquartile range (IQR, 15, 60%) for euthyroid sick syndrome (ESS) vs 25% IQR (10, 40) for non-ESS ($P < .05$). *B,* Kaplan-Meier curve for mortality in patients with COVID-19 with ESS vs patients without ESS with lung involvement by COVID 19 changes by 50% or less ($P = .00417$). *C,* Kaplan-Meier curve for mortality in patients with COVID-19 with ESS vs patients without ESS with lung involvement by COVID-19 changes by more than 50% ($P = .19333$). *CT =* computed tomography.

to COVID-19. Our results indicate that special attention and more intensive surveillance should be considered for patients with COVID-19 with ESS.

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Disclosure

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