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ORIGINAL PAPER

Nonthyroidal illness syndrome as independent predictor of hospital mortality in the elderly hospitalized patients with COVID-19 pneumonia – single-center observation

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ABSTRACT

Introduction and aim. Elderly patients with COVID-19 are at increased risk for adverse outcomes. This study aims to evaluate the prevalence of nonthyroidal illness syndrome (NTIS) in hospitalized patients with COVID-19 pneumonia, its independent impact on patients' survival. Furthermore, to investigate selected inflammatory biomarkers in those patients and to determine whether they predict mortality associated with the disease.

Material and methods. In this single-centered, retrospective study, the medical records of 53 patients with confirmed SARS-CoV-2 infection who attended the provincial hospital between October 2020 and January 2021 were reviewed. Demographic data, laboratory values, comorbidities, treatments, and clinical outcomes were collected. We compared the data in survivor and non-survivor groups.

Results. Of 393 adult patients with SARS-CoV-2 pneumonia, 53 (13,49%) met the inclusion criteria and were included. The median age was 72±12.2 years, 26 patients (49%) were men. The NTIS prevalence was 62.3% and showed a strong independent correlation with disease severity and mortality in COVID-19 patients (p=0.01). The interleukin-6, white blood cells, ferritin and neutrophil ratios also differed significantly statistically between survivors and non-survivors.

Conclusion. NTIS and the lowering level of FT3 pose an independent prognostic marker of clinical deterioration and higher mortality in elderly patients with COVID-19.

Keywords. COVID-19, elderly, mortality, NTIS, pneumonia

Introduction

COVID-19 is an acute infectious disease of the respiratory system caused by the coronavirus of the severe acute respiratory syndrome (SARS-CoV-2). Most patients have mild symptoms and recover without special treatment. However, some of them develop serious complications and need hospital care. Most of the patients requiring hospitalization due to COVID-19 pneumonia constitute the geriatric population. Infection-hospitalization ratio estimates ranged from 0.4% for those younger than 40 years to 9.2% for those older than 60 years.[1] The mortality rate for patients with COVID-19 admitted to hospitals is high.[2] SARS-CoV-2 is known to have direct effects on endocrine glands, including the pituitary and thyroid gland. The virus has been detected in the pituitary gland after mortem. The hypothalamic-pi-

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tuitary-thyroid axis may be one of the most susceptible to disturbance in patients with COVID-19.[3] The mRNA of the SARS-CoV-2 receptor, ACE-2 is expressed in thyroid cells.[4] Three main mechanisms for thyroid function disorders in patients with COVID-19 are: a direct viral effect on thyroid cells; an indirect effect of the systemic inflammatory immune response; and the most common thyroid dysfunction in the shape of Non-thyroidal illness syndrome (NTIS).[4] NTIS also known as "sick euthyroid syndrome or low T3 syndrome" is usually described as a transient biochemical deviation of thyroid hormone levels and is common in the hospitalized older population with acute or chronic critical illness. About 93% of total triiodothyronine (T3) is produced by the peripheral conversion from total thyroxine (T4) so this syndrome is considered to be a condition with impaired peripheral conversion of T4 to T3.[5,6]

One of the theories of the NTIS pathogenesis in COVID-19 includes suppression of hypothalamic thyrotropin-releasing hormone, and as a result reduced secretion of TSH. Sometimes distinguishing between NTIS and central hypothyroidism can be difficult.[7] We still do not know whether hormone responses represent an adaptive, physiological response or they are a maladaptive response that contributes to the worsening of the disease.[8]

The most common hormone pattern in NTIS is low T3 and free triiodothyronine (FT3) with low or normal free thyroxine (FT4) and normal or decreased levels of thyrotropin (TSH). The elevated plasma reverse (rT3) may occur.[9]

The mechanism of this syndrome is not yet well defined, so there is controversy about the indication of the treatment of this condition with hormone replacement therapy.[10] Sciacchitano et al. indicated the method which could represent the system in recognizing the efficacy of T3 treatment in NTIS.[11] NTIS occurs more frequently among patients with more severe COVID-19. It is clinically relevant whether the occurrence of NTIS on admission predicts adverse clinical outcomes in COVID-19 patients and whether this syndrome can be useful for clinicians in comprehensive geriatric assessment for management decisions.[12] Despite many studies, the prognostic role of thyroid hormone abnormalities in older patients remains uncertain.

Aim

The aim of this study was to investigate the frequency of NTIS in hospitalized elderly patients with COVID-19 pneumonia and to evaluate if it is an independent risk factor of the deterioration and mortality of those patients. Furthermore, we were additionally looking for the role of selected inflammatory biomarkers and their independent impact on patient's survival.

Material and methods

Ethics approval

This retrospective study was approved by the Bioethics Committee of the University of Rzeszów (Reference No. 12/05/2020). The procedures used in this study adhere to the tenets of the Declaration of Helsinki. We collated data mainly from electronic patient histories. Although personal identification numbers were used to match the datasets, these were subsequently anonymized.

Study desing

We retrospectively analyzed laboratory data from patients hospitalized in St. Queen Jadwiga Clinical District Hospital No. 2 Rzeszów, in the Department of Internal Medicine, Nephrology, and Endocrinology from October 2020 to January 2021 with confirmed SARS-CoV-2 infection (n=393). For this analysis, we selected the data of 53 patients (13.49%) with COVID-19 pneumonia. Hospitalization due to COVID-19 pneumonia was the criterion for inclusion in the study. All patients were tested positive for SARS-CoV-2 using real-time reverse transcriptase-polymerase chain reaction (RT-PCR) with samples from the respiratory tract, throat, and nose swab. All of them were symptomatic and showed common respiratory tract symptoms such as dyspnea, cough, or gastric symptoms of COVID-19.

Table 1. Biochemical blood parameters tested at the hospitalization, the methodology of determinations and the range of reference values*

Findings	Reference range	Determination method
FT3, pg/mL	2.3–4.2	chemiluminescent immunoassay CLIA
FT4, ng/dL	0.89–1.76	
TSH, uIU/mL	0.55–4.78	
WBC, 10^9/L	4–11	fluorescence flow cytometry using a laser
Neutrophils, 10^9/L	1.9–7.5	
Lymphocytes, 10^9/L	0.9–4.5	
CRP, mg/L	< 10	immunoturbidimetry
Ferritin, ng/mL	10–291	chemiluminescent immunoassay CLIA
Interleukin-6, pg/mL	< 4.4	
PCT, ng/mL	< 0.03	

* Abbreviations: FT3 – free triiodothyronine; FT4 – free thyroxine; TSH – thyrotropin; CRP – C-reactive protein; PCT – procalcitonin; WBC – white blood cell count, CLIA – clinical laboratory improvement amendments

All patients with COVID-19 infection were initially in stage II of the course of the disease.[13] Patients with a history of thyroid disease, patients treated with thyroid drugs, and those who recently received iodinated contrast were excluded. Most of the patients eligible for the study had comorbidities, the most common being

hypertension (n=44, 83%), heart disease (n=32, 60.4%) (including coronary artery disease, condition after myocardial infarction or coronary angiography with coronary artery bypass surgery, heart failure or arrhythmias) and diabetes (n=22, 41.5%). Each patient had blood tests at the beginning of hospitalization, before initiation of COVID-19 treatments. Laboratory tests were performed in the hospital laboratory. All patients were treated for COVID-19 in accordance with the recommendations of the Polish Association of Epidemiologists and Infectiologists in the period from October 2020 to January 2021.[14,15]

Table 1 presents the biochemical parameters tested in the blood serum at the beginning of hospitalization, the methodology of determinations, and the range of reference values.

Statistical analysis

Statistical analysis was performed with the STATISTICA 13.1 statistical program (StatSoft Inc. 2016, Tulsa, OK, USA). Differences between categorical variables were evaluated using Pearson's Chi-square test. Yates' correction was used at frequencies lower than five. The Shapiro-Wilk test was used for the assessment of the distribution of continuous variables. Due to non-normal distribution, continuous variables were compared using Mann Whitney's U test for two groups, or Kruskal-Wallis one-way analysis of variance with additional post hoc comparisons for three or more groups. A correction for multiple tests was applied. Correlations between variables were measured for normal distribution with Pearson's correlation, otherwise with Spearman's correlation, p values < 0.05 were considered statistically significant.

Results

The final study population included 53 patients with a laboratory-confirmed presence of SARS-CoV-2 RNA and CT confirmed COVID-19 related pneumonia. The median age was 72±12.2 years, 26 patients (49%) were men. The 45 (84.9%) of included patients were elderly persons according to classification.[16] All deaths due to COVID-19 pneumonia were over the age of sixty. The 51 (96%) patients had chronic diseases. The demographic and clinical characteristics of all included patients divided into non-survivors and survivors are presented in Table 2.

Table 3 presents the relationship between thyroid hormones (TH) levels, selected inflammatory markers and in-hospital mortality of patients with COVID-19 pneumonia.

Our analysis showed the appearance of NTIS in 33 (62.3%) of all patients, 11 (33.3%) of whom died. Based on statistical analysis, serum levels of FT3 were observed to decrease and showed a strong independent correlation with disease severity and mortality prognosis in COVID-19 patients. The observed relationship is presented in Figure 1.

Table 2. Selected demographic and clinical data results in survivors and non-survivors of COVID-19 patients*

Parameter	Non-survivors (n=14)	Survivors (n=39)	p
Demographics, n (%)			
Male sex	7 (50%)	19 (48.72%)	0.93
Female sex	7 (50%)	20 (51.28%)	
Age, median years (min-max)	79.5 (60–91)	72 (37–90)	0.06
< 60	0	8 (20.51%)	0.16
60 +	14 (100%)	31 (79.49%)	
Comorbidities, n (%)			
Hypertension	11 (78.57%)	33 (84.62%)	0.92
Heart disease	13 (92.86%)	19 (48.72%)	0.01
COPD	2 (14.29%)	5 (12.82%)	0.75
T2DM	4 (28.57%)	18 (46.15%)	0.41
CKD	8 (57.14%)	8 (20.51%)	0.01
Drugs used, n (%)			
Metformin	2 (14.29%)	5 (12.82%)	0.75
Insulin	6 (42.86%)	12 (30.77%)	0.41
ACE-I	6 (42.86%)	20 (51.28%)	0.59
ARB	1 (7.14%)	1 (2.56%)	0.96

*Abbreviations: COPD – chronic obstructive pulmonary disease; CKD – chronic kidney disease; T2DM – diabetes mellitus type 2; ACE-I – angiotensin converting enzyme inhibitors; ARB – angiotensin receptor blockers; p < 0.05 was considered statistically significant

Table 3. Relationship between TH levels, selected inflammatory markers and in-hospital mortality of patients with COVID-19 pneumonia*

Predictive parameter	Non-survivors (n=14)			Survivors (n=39)			p
	median	min.	max.	median	min.	max.	
FT3, pg/mL	1.8	1.2	2.5	2.2	1.3	3.4	0.01
FT4, ng/mL	1.1	0.6	1.5	1.3	0.6	1.8	0.05
TSH, uIU/mL	0.8	0.2	3.2	0.7	0.2	2.8	0.37
Interleukin 6, pg/mL	41.9	4.8	620	15	2.7	559	0.05
CRP, µmol/L	76	4	159	49	4	366.2	0.39
PCT, ng/mL	0.165	0.05	2	0.11	0.003	17	0.16
Ferritin, ng/mL	221.25	22	994	570	12	16000	0.01
WBC, 10^9/L	10.9	7.78	195	6.75	1.01	25.97	0.002
Neutrophils, cells/µL	7860	752	15050	5120	897	23770	0.04
Lymphocyte, cells/µL	1020	210	2150	950	10	11210	0.99

*Abbreviations: FT3 – free triiodothyronine; FT4 – free thyroxine; TSH – thyrotropin; CRP – C-reactive protein; PCT – procalcitonin; WBC – white blood cell count; min. – minimum; max. – maximum

The lowered FT3 level was statistically significant (p=0.01). The FT4 levels were marginally lower in the non-survivors compared to survivor patients (p=0.05). Spearman's correlations between FT3 and the age of pa-

tients was statistically significant (R = -0.31). The observed relationship is presented in Figure 2.

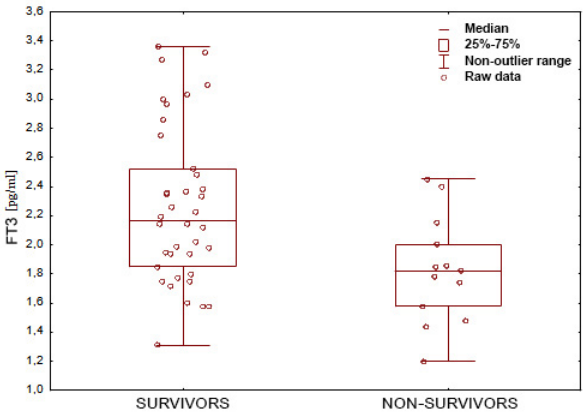

Fig. 1. Relationship between the level of FT3 and mortality in patients with COVID-19 pneumonia

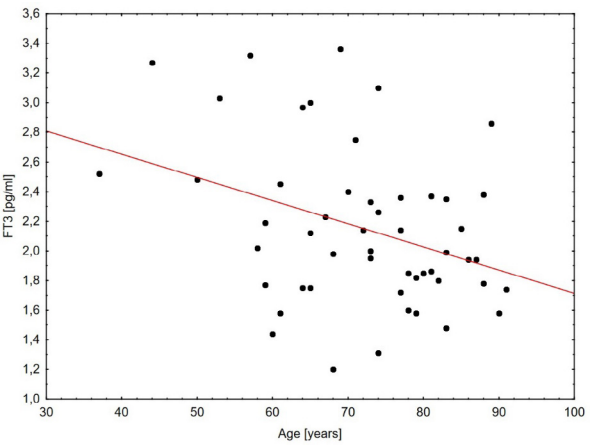

Figure 2. Relationship between the level of FT3 and age in patients with COVID-19 pneumonia

The risk of in-hospital death in elderly COVID-19 patients was also higher for the increasing values of selected inflammatory markers (Table 3). It was observed that WBC (p=0.002), neutrophils (p=0.04) and IL-6 (p=0.05) could be predictors of deterioration patients with COVID-19. The median Il-6 for deceased patients was statistically significantly higher than for those who survived (41.9 pg/mL and 15 pg/mL, respectively). These markers can also be useful in the assessment of the risk of death.

The relationship between Il-6 and mortality in patients with COVID-19 pneumonia is shown in Figure 3.

Unexpectedly a decrease in ferritin was observed in non-survivor elderly patients with COVID-19 pneumonia compared to survivors (p=0.01). There were no statistically significant differences in the level of CRP and PCT between survivors and non-survivors in our study.

In the tested sample, the relationship between lymphocytes and FT3 was also not statistically significant (Spearman's rank order correlation R = 0.13 p> 0.05).

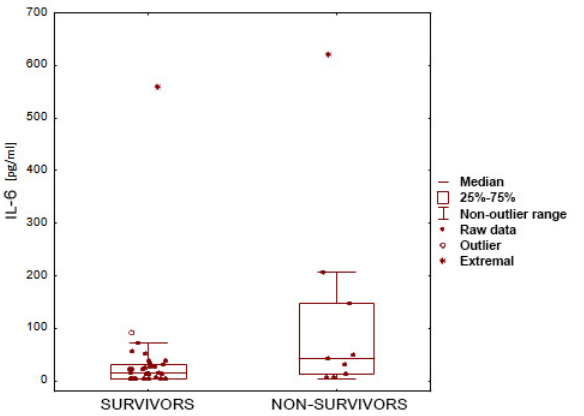

Figure 3. Relationship between Il-6 and mortality in patients with COVID-19 pneumonia

Discussion

Most of the patients requiring hospitalization due to COVID-19 pneumonia constitute the geriatric population. Some of the risk factors for mortality reported in patients with COVID-19, except age, are male gender, duration from onset to admission, admission SARS-CoV-2 viral load, comorbidities and higher levels of inflammatory markers.[17,19-21] The study by Alizadehsani et al. indicate that age, blood group, heart disease, anosmia and dry cough are the most crucial factors in the mortality of patients with COVID-19.[18] The coexistence of chronic diseases, poor physical condition, lymphopenia, bacterial co-infection and smoking history also increase the ratio of death.[21,22] Many factors influence the thyroid function during COVID-19 infection. Hypercortisolemia, increased cytokines, oxidative stress can impact on thyroid axis.[23,24] Several of the commonly used medications, such as glucocorticoids, dopamine or heparin, may affect or interfere with thyroid function tests.[25,26] Patients with COVID-19 often require such treatment. Therefore, thyroid function was measured, before treatment in the enrolled patients.

It is still not clear whether the finding of low FT3 levels in patients with COVID-19 describes NTIS or if the thyroid could be a direct target of SARS-CoV-2. Wang et al. found that the TSH level of COVID-19 patients was significantly lower than that in non-COVID-19 pneumonia patients and this suggests that thyroid function abnormalities in COVID-19 patients cannot be fully explained by NTIS.[27] The mRNA encoding for the ACE-2 receptor is expressed in follicular thyroid cells, making them a potential target for SARS-COV-2 entry.[28] The potential effect of systemic inflammation on thyroid is also accent.[27,29] The inflammatory response leads among others to a reduction in deiodinase activity and a decrease in the conversion of T4 to T3. In a study by Ilera et al. all TH (T3, T4, FT3, FT4) correlated, in an opposite way, with in-

flammation parameters and worse clinical outcome.[29] The suppression of the hypothalamic-pituitary-thyroid axis is also observed.[7] Some scientists reported that the elevated C-reactive protein was independently associated with the appearance of low TSH and low FT3.[30,31] Wang et al. identified increased levels of leukocytes, neutrophils, CRP and procalcitonin, and decreased levels of lymphocytes in the thyroid dysfunction group.[27]

We did not observe a statistically significant correlation between inflammatory markers (IL-6, CRP, lymphocyte levels) with NTIS in our study. These discrepancies may have been due to the small size of our group or the age-related decreasing of immune response (84.9% of patients were over 60 years of age), but other factors should be taken into account. NTIS does not always correlate with inflammatory markers. Lui et al. reported that NTIS on admission could predict clinical deterioration in COVID19 patients, irrespective of SARS-CoV-2 viral load, age and markers of inflammation and tissue injury.[12,30]

The interesting studies analyzed thyroid function between COVID-19 patients and healthy control, and reported the potential prognostic role of low FT3, mainly in severe COVID19 pneumonia. The serum TSH and T3 levels in COVID-19 patients were significantly lower than those of the healthy group. The degree of the decrease in TSH and T3 correlated positively with the severity of COVID-19 disease.[32-35] A study by Khoo et al. detected that patients with COVID-19 had lower admission levels of TSH and FT4.[36] We noticed that low serum FT3 levels showed a strong independent correlation with disease severity and mortality in COVID-19 patients (p=0.01). Many patients with the lower FT3 levels at hospital admission had deteriorated and died, which is in line with the data from the literature.

Serum FT3 concentration is lower in patients with severe COVID-19 and appears to be associated with an increased risk of death in COVID-19 patients, so it could be a potential independent prognostic marker at hospital admission.[37-39]

NTIS is common and significantly related to mortality in acutely ill, hospitalized old patients. Thyroid hormones, especially serum FT3 determination may predict clinical outcomes in old, frail patients and perhaps they should be included in the assessment of short-term prognosis.[40,41] However, the ascertainment of a definite prognostic role of NTIS in older patients with COVID-19 is difficult because this syndrome may be due to comorbidities, not only by COVID-19 pneumonia.[42]

The inflammatory response plays an important role in the progression of COVID-19. Several inflammatory markers have been reported to be associated with the severity of COVID-19.[31] The analysis of inflammatory markers (regardless of NTIS) in our group of patients showed that IL-6, WBC and neutrophil levels are significantly higher in severe COVID-19 patients, which is comparable with the available literature.[43-45] In our study, lower ferritin is associated with increased mortality of patients. This finding is in contrast with the findings of a systematic review by Cheng et al.[46]

This discrepancy could be explained by high frequency of age-related iron deficiency in our patients or population differences.[47]

There are several limitations to our study. First, it is a retrospective and unplanned work, and most of the data was obtained from electronic patient histories. Second, applying the exclusion criteria, the study sample was not large. Third, reverse triiodothyronine was not measured, therefore partial central hypothyroidism and NTIS were difficult to distinguish.

Finally, elderly patients, especially those with comorbidities, have a high incidence of NTIS and it is difficult to determine to what extent this syndrome is due to COVID-19 pneumonia alone.

Conclusion

Our study provides data that validate the prognostic role of low levels of FT3 in COVID-19 patients. We have shown that low serum FT3 is an important independent mortality risk factor in elderly patients with COVID-19 pneumonia. Serum FT3 determination could be included in the assessment prognosis of elderly patients with COVID-19 pneumonia.

Our findings confirms that the levels of Il-6, WBC, ferritin and neutrophils are also the valuable bioindicators of in-hospital mortality in patients with COVID-19. This study may be helpful in early prediction and risk reduction of mortality in elderly patients infected with COVID-19.

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Declarations

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Author contributions

Conceptualization, A.M. and R.O.F.; Methodology, R.O.F., A.M., A.C.W., A.G.B.; Software, K.G.; Formal Analysis, A.M., R.O.F., A.C.W.,A.G.B.,K.G.; Investigation, A.M, R.O.F., A.C.W.; Resources, A.M., A.C.W., R.O.F.; Data Curation, A.M., A.C.W., R.O.F., Writing – Original Draft Preparation, A.M., R.O.F., A.C.W., A.G.B.; Writing – Review & Editing, A.M.,R.O.F.,A.G.B.; Visualization, K.G.; Supervision, R.O.F.,A.G.B.; Project Administration, R.O.F.

Conflicts of interest

The authors declare no competing interests.

Data availability

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval

This retrospective study was approved by the Bioethics Committee of the University of Rzeszów (Reference No. 12/05/2020). The procedures used in this study adhere to the tenets of the Declaration of Helsinki. We collated data mainly from electronic patient histories. Although personal identification numbers were used to match the datasets, these were subsequently anonymized.

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