




Is non-thyroidal illness syndrome (NTIS) a clinical predictor of COVID-19 mortality in critically ill oldest old patients?

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Introduction

The spread of Coronavirus disease (COVID-19) has caused a global pandemic, with severe social and economic consequences worldwide. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) binds the human angiotensin converting enzyme-2 (ACE-2) receptors to enter into the host cells, determining multiple organ damage, including acute lung injury. Evidence so far suggests that SARS-CoV-2 may affect various endocrine organs, in children [1] and in the older, including thyroid cells, and possibly inducing non-thyroidal illness, producing inflammation and dysfunction by direct virus damage, indirect effect on the hypothalamus-pituitary gland axis, systemic inflammation and cytokine storm [2]. Previous studies have reported a high prevalence of non-thyroidal illness syndrome (NTIS) in COVID-19, associated with poor outcomes [2, 3]. NTIS is a common disorder in older people, its prevalence increasing with advancing age, regardless the pathogen implied [4]; in different phases of critical illnesses could vary [5], as seen in COVID-19 patients admitted for pneumonia or requiring intensive care unit [3]. Notwithstanding, few studies have specifically attempted to evaluate the different prognostic impact of NTIS in COVID-19 and non-COVID-19 pneumonia [6]. The aim of the current study was to verify the impact of NTIS on short-term mortality in two cohorts of older patients respectively hospitalized for COVID-19 and non-COVID-19 pneumonia.

Materials and methods

In the present observational, single-center study we performed a post-hoc analysis of a cohort of older patients hospitalized for non-COVID-19 pneumonia admitted to our Geriatrics Unit from July 2018 to January 2019 [7], and data collected from a cohort of older patients consecutively hospitalized for COVID-19 pneumonia from April to March 2020. In both the cohorts, demographic characteristics and clinical history were obtained at admission; Charlson comorbidity index [8] was reported to evaluate the patients' burden of comorbidities. At enrolment, patients taking lithium, iodine, amiodarone, barbiturates, dopaminergic drugs, non-selective beta blockers, antiepileptic drugs and any thyroid therapy were excluded; moreover, all the CT scans were done without iodinated contrast medium. All the patients underwent clinical examination and blood testing. Blood was drawn the morning following hospital admittance, after an overnight fast and before receiving any prescribed therapy, including steroids. Serum TSH, FT3, and FT4 were measured by immunometric technique (Ortho-Clinical Diagnostics, Amersham, UK). Normal values for TSH, FT4, and FT3 were as follows: 0.4–4.0 mIU/L, 0.70–1.70 ng/dL, and 2.7–5.7 pg/mL, respectively. Pneumonia severity was classified according to the ARDS criteria of the Berlin task force [9]. Patients were classified as NTIS when showing low free triiodothyronine (FT3), normal or low free thyroxin (FT4) and normal or low TSH values [4]. Given that glucocorticoid excess affects the hypothalamus–pituitary–thyroid axis by reducing secretion and activity of thyroid hormones, we have also analyzed the sub-group of patients not receiving corticosteroid therapy at admission. SARS CoV-2 infection was confirmed by PCR nasopharyngeal swab test. All the patients underwent either chest X-ray or computed tomography to diagnose acute pneumonia. We performed

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post-discharge follow-up, assessing both in-hospital and one-month mortality in both the cohorts by telephone interview. Written informed consent was obtained from all the patients or the legally authorized delegate when patients temporarily or permanently without capacity. The study protocol complied with the Declaration of Helsinki and was approved by the Pisa University Hospital Ethic Committee (approval number 17241 20/04/2020).

Results

Overall, 176 inpatients were included in the study analysis, ninety-five patients admitted for acute COVID-19 pneumonia (47.4% women; mean age 81.9 ± 7.8 years) and 81 patients previously hospitalized for non-COVID-19 pneumonia (46.9% women; mean age 85.2 ± 6.6 years). Compared to non-COVID-19 patients, those with COVID-19 pneumonia showed lower levels of high sensitivity C-reactive protein (hs-CRP: 8.3 ± 6.4 vs 13.4 ± 8.5 , $p = 0.002$). Patients were also stratified per pneumonia severity (Table 1). Of note, thirty-one patients with COVID-19 were receiving oral systemic corticosteroid therapy (OSC) at hospital admission, while none of the

patients in the non-COVID-19 subgroup received daily OSC therapy before hospitalization. As shown in Table 1, NTIS was diagnosed in 63 (66.3%) patients with COVID-19 and in 55 (67.9%) with non-COVID-19 pneumonia ($p = 0.82$). In the COVID-19 group, patients with NTIS were older than non-NTIS (83.3 ± 6.3 vs 79.1 ± 9.6 respectively, $p = 0.011$), at odds with the non-COVID-19 group, in which mean age did not differ between the NTIS and non-NTIS-subgroups (84.8 ± 6.9 vs 85.8 ± 6 respectively, $p = 0.57$) (Table 2). In the whole cohort, NTIS patients showed a higher number of comorbidities as compared to non-NTIS [CCI: 5.6 ± 2.4 vs 4.6 ± 2.5 , respectively; $p = 0.021$ (COVID-19 group) and 6.2 ± 2.8 vs 4.5 ± 2.1 , $p = 0.014$ (non-COVID-19 group)]. As a whole, patients with COVID-19 pneumonia showed a significantly higher overall mortality as compared to non-COVID-19 ones (26.3% vs 11.1%, $p = 0.01$). In detail, among COVID-19 patients, a slightly lower overall mortality of NTIS patients as compared to non-NTIS was observed (23.8% vs 31.2% respectively, $p = 0.43$), while non-COVID-19 patients with NTIS showed a three times higher mortality than non-NTIS, although without reaching the statistical significance (14.5% vs 3.8% respectively, $p = 0.09$). Once excluded patients prescribed with oral corticosteroids

Table 1 Differences on thyroid dysfunction between COVID-19 and non-COVID-19 pneumonia older patients

	COVID-19 pneumonia (N=95)	Non-COVID-19 pneumonia (N=81)	<i>p</i> value
Age, Years	81.9 (± 7.8)	85.2(± 6.6)	0.005
Sex (F)	45 (47.4%)	38 (46.9%)	0.95
WBC, $10^3/\text{mcL}$	9869 ($\pm 14,570$)	12,430 (± 4805)	0.13
Hs-CRP, mg/dL	8.3 (± 6.4)	13.4 (± 8.5)	0.002
PaO ₂ /FiO ₂ ratio	208 (± 109)	246 (± 62)	0.13
CCI	5.3 (± 2.5)	5.8 (± 3.2)	0.24
TSH, mIU/L	1.75 (± 4.02)	1.63 (± 2.59)	0.81
FT3, ng/dL	2.37 (± 0.61)	2.40 (± 0.60)	0.73
FT4, pg/dL	1.45 (± 0.45)	1.50 (± 0.48)	0.48
NTIS (%)	63 (66.3%)	55 (67.9%)	0.82
No ARDS	26.5%	13.3%	<0.001
Mild ARDS (200 mmHg \leq PaO ₂ /FiO ₂ < 300 mmHg)	28.9%	66.3%	
Moderate ARDS (100 mmHg \leq PaO ₂ /FiO ₂ < 200 mmHg)	19.3%	19.3%	
Severe ARDS (PaO ₂ /FiO ₂ < 100 mmHg)	25.3%	1.2%	
Overall mortality (%) (whole cohort)	25 (26.3%)	9 (11.1%)	0.01
Patients without OCS therapy at admission	16 (25.4%)	9 (11.1%)	0.03

Data are shown with percentages for categoric variables, mean (standard deviation) for continuous variables. Significant *p* values are in bold

CCI Charlson Comorbidity Index, Hs-CRP high sensitivity C-reactive protein, NTIS non-thyroidal illness syndrome. PaO₂/FiO₂ ratio of arterial oxygen partial pression to fractional inspired oxygen, WBC white blood cells, OCS oral corticosteroids, ARDS acute respiratory distress syndrome

Table 2 Clinical features of NTIS COVID-19 patients versus non-NTIS patients

	COVID-19 patients (n=95)	NTIS (n=63)	Non-NTIS(n=32)	p value	Non-COVID-19 patients (n=81)	NTIS (n=55)	Non-NTIS (n=26)	p value
Age (years)	81.9 (±7.8)	83.3 (±6.3)	79.1 (±9.6)	0.011	85.2 (±6.6)	84.8 (±6.9)	85.8 (±6.0)	0.57
Sex (F)	45 (47.4%)	32 (50.8%)	13 (40.6%)	0.34	38 (46.9%)	22 (57.9%)	16 (42.1%)	0.70
CCI	5.3 (±2.5)	5.6 (±2.4)	4.6 (±2.5)	0.021	5.8 (±3.2)	6.2 (±2.8)	4.5 (±2.1)	0.014
TSH (mIU/L)	1.75 (±4.02)	1.02 (±0.85)	3.47 (±7.02)	0.008	1.63 (±2.59)	1.00 (±0.75)	2.9 (±4.14)	0.001
FT3 (ng/mL)	2.3 (±0.16)	2.12 (±0.36)	2.94 (±0.69)	<0.001	2.40 (±0.60)	2.12 (±0.41)	2.96 (±0.54)	0.001
FT4 (pg/mL)	1.45 (±0.46)	1.47 (±0.47)	1.42 (±0.443)	0.65	1.50 (±0.48)	1.51 (±0.47)	1.49 (±0.50)	0.886
WBC (10 ³ /mcL)	9869 (±14,570)	8136 (±3577)	13,280 (±24,497)	0.31	12,430 (±4805)	12,220 (±4701)	12,860 (±5086)	0.57
Hs-CRP, (mg/dL)	8.3 (±6.4)	8.9 (±6.5)	6.5 (±5.9)	0.08	13.4 (±8.5)	16 (±8.4)	12.2 (±8.5)	0.03
Baseline PaO ₂ /FiO ₂ ratio	208 (±109)	206 (±113.1)	222 (±105.8)	0.506	246 (±62)	243.5 (±64.1)	248.5 (±58.8)	0.650
Overall mortality	25(26.3%)	15 (23.8%)	10 (31.2%)	0.43	9 (11.1%)	8 (14.5%)	1 (3.8%)	0.09
Intra-hospital mortality	15 (15.8%)	9 (14.3%)	6 (18.8%)	0.72	5 (6.1%)	4 (7.2%)	1 (3.8%)	0.54
Short-term (30 days) overall mortality	10 (17.5%)	6 (16.2%)	4 (20.0%)	0.47	4 (5.2%)	4 (7.8%)	0 (0)	0.30
Overall mortality of patients without OCS therapy at admission	16 (25.4%)	10 (21.7%)	6 (32.0%)	0.34	9 (11.1%)	8 (14.5%)	1 (3.8%)	0.09

Data are shown with percentages for categorical variables, mean (standard deviation) for continuous variables. Significant *p* values are in bold. CCI Charlson Comorbidity Index, Hs-CRP high sensitivity C-reactive protein, NTIS non-thyroidal illness syndrome. PaO₂/FiO₂ ratio of arterial oxygen partial pressure to fractional inspired oxygen, WBC white blood cells, OCS oral corticosteroids

(OCS) therapy at admission, the prevalence of NTIS and the overall mortality did not change (Tables 1 and 2).

Discussion

In our study, almost two-third of older patients with pneumonia had a diagnosis of NTIS, without significant difference between COVID-19 and non-COVID-19 patients, at odds with previous studies indicating an increased prevalence of NTIS in SARS-CoV-2 infection [2], possibly due to the cytokine storm reported in literature [2]. COVID-19 patients showed over than two-fold higher overall mortality than those with non-COVID-19 pneumonia, regardless lower mean age and comorbidity burden. This finding is not surprising since COVID-19, at least the first pandemic waves, is characterized by extreme lethality in older adults. Of note, COVID-19 patients showed lower Hs-CRP levels than those with non-COVID-19 pneumonia, probably due to the high prevalence of corticosteroid therapy at admission in the COVID-19 cohort, which may attenuate CRP synthesis in critically ill patients. Interestingly, the two cohorts exhibited opposite trends of short-term mortality. Indeed, although

not reaching statistical significance, non-COVID-19 patients with NTIS showed three-times higher overall mortality than non-NTIS, whereas COVID-19 patients with NTIS resulted less likely to die, also while excluding patients receiving OCS at admission. Superimposable mortality trends were obtained evaluating intra-hospital and 30-day post-discharge overall mortality separately.

At odds with our results, a recent meta-analysis showed that serum free thyroid hormone and TSH levels were inversely correlated with COVID-19 severity, and the mortality of COVID patients with NTIS was significantly higher than that of non-NTIS patients [2]. Interesting results come from patients with COVID-19 hospitalized for pneumonia or needing intensive-care support [3]; however, none of the previous studies evaluated specifically oldest old patients hospitalized in acute geriatrics wards. Although NTIS correlated with the burden of comorbidity and the degree of inflammation in both cohorts, a likely explanation of our rather surprising finding may be the significantly higher severity of COVID-19 pneumonia, which may minimize the clinical impact of NTIS in oldest old patients, especially in those with moderate to severe respiratory failure, representing almost the half of the entire COVID-19 pneumonia

cohort [9]. We acknowledge that the cohort of patients is small, especially after excluding the ones prescribed with OCS before admission, and that the comparative cohort of not-COVID-19 pneumonia is not contemporary, although homogenous in terms of thyroid function, CCI and sex. This limitation must be taken into account when interpreting our results, which certainly underline the need of further and larger dataset, to either confirm or confute them, in such a peculiar group of frail patients.

In conclusion, NTIS emerged as the most prevalent thyroid alteration in oldest old inpatients with COVID-19 pneumonia but, possibly due to its extremely high lethality, those with NTIS did not show higher mortality risk.

Declarations

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

Ethical approval The study protocol complied with the Declaration of Helsinki and was approved by the Pisa University Hospital Ethic Committee (approval number 17241 20/04/2020).

Informed consent Written informed consent was obtained from all the patients or the legally authorized delegate when patients temporarily or permanently without capacity.

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