LETTER TO EDITOR / CARTA AL EDITOR

EndoCovid: Thyroid and adrenal hormonal alterations in a cohort of critically ill patients with COVID-19. A preliminary analysis

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Coronavirus disease 2019 (COVID-19) infection was primarily described as atypical pneumonia with severe respiratory disorders[1], although the reported evidence revealed a condition of multisystemic impact over time. It maintains a variable respiratory severity that significantly affects other organs and systems, such as the vascular endothelium, the central nervous system, the heart, and many endocrine glands such as the thyroid, the adrenals, and the pancreas[2]. The impact of SARS-Cov-2 on the endocrine system is so frequent that specialists have coined the term "EndoCovid" to refer to the endocrinological disorders that occur during this disease and require special attention in post-COVID 19 patients[3]. The universal distribution of the angiotensin 2 receptor (ACE-2), which is the proven gateway for the virus to enter our cells, makes the viral presence in glandular tissue possible and causes damage by three fundamental mechanisms: direct damage immunological mechanism and functional alteration[4,5]. Specifically, it has already been demonstrated with SARS-Cov-1 and currently with SARS-Cov-2, damage at the pituitary level[6], with hypophysitis reported in autopsies[7]. This alteration leads to secondary hypopituitarism that must be considered for its diagnosis and treatment, emphasizing cortisol deficiency, which often debuts hyponatremia, a condition associated with a poor prognosis[6]. The virus can also cause direct damage to the thyroid (COVID-19-associated thyroiditis and post-COVID-19 or post-vaccination autoimmune thyroid pathology) and the adrenal glands, which is associated with severe forms of the disease although the impact of this disorder in outcomes such as mortality is not clear[8]. Several of the critically ill patients that we attended with a diagnosis of severe COVID-19 infection, who had overcome the hypoxemia, were noticed to worsen and died after day 10 of hospitalization. A non-pharmacological distributive shock with negative bacterial cultures was determined as their cause of death. Under this premise, we requested the adrenal and thyroid hormones dosage, observing a significant hormonal deficit. The subsequent compensation of the endocrine disorder meant a significant clinical improvement and even survival of patients whose clinical characteristics and severity scales pointed to a high probability of death. We present a series of 66 patients with severe COVID-19 infection, where 28 (42.4%) died, and 38 (57.6%) survived; the patient's average age was 47.74 years, with differences being observed when comparing by discharge condition (p-value 0.024, 51.79 years in non-survivors vs. 44.76 years in survivors); male predominance was observed 81.82%. (Table 1).

Thyroid and adrenal alterations were observed in 59.09% and 68.18% of the patients. In addition, when comparing mortality between the presence or absence of thyroid and adrenal alterations, no significant differences were observed, which can be explained by the indicated hormonal replacement (adrenal and thyroid replacement were 63.64% and 62.12%, respectively). This would also explain the absence of difference in electrolyte disturbances, fever, eosinophil count and shock. Methylprednisolone was the primary corticosteroid used in adrenal hormone replacement (68.18%), and levothyroxine in thyroid replacement. The median number of days of mechanical ventilation was 8, while hospitalization stays was10 days. The hospital stay presented significant differences by discharge condition (p-value 0.049, 9 days in non-survivors vs. 12 days in survivors). (Table 2).

When comparing the median cortisol levels of COVID-19 patients at admission and 6 days later, significant differences were observed (p-value <0.001, 2.24 mcg/dL at admission vs 17.88 mcg/dL.at day 6). The data indicate that hormone replacement was effective in normalizing the adre-

Demographic characteristics	Total	Discharge condition		p-value
		Non survivor	Survivor	
Age (mean (SD))[1/]	47,74 (12,55)	51,79 (12,36)	44,76 (11,99)	0,024*
Sex (n (%))[2/]				
Male	54 (81,82)	24 (44,44)	30 (55,56)	0,481
Female	12 (18,18)	4 (33,33)	8 (66,67)	

Note: SD=standard deviation; * significance, 1/ t test, 2/Chi-square test

Table 1. Demographic characteristics by discharge condition.

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nal profile. (Figure 1).

When comparing the TSH values between patients with and without thyroid alteration, significant differences were observed (p-value <0.001, 0.26 µIU/mL for those with alteration vs. 1.11 µIU/mL for those without alteration) (Figure 2), but no significant differences were observed for T4 levels (Figure 3), which indicates that thyroid involvement is predominantly central in this series. Median cortisol values showed significant differences in the presence or absence of adrenal alteration (p-value <0.001, 2 mcg/dL in the presence of alteration vs. 17 mcg/dL in the absence). (Figure 4)

Conclusions

Based on the above, we can infer that endocrinological alterations associated with COVID-19 infection are frequent and probably more prevalent in patients who progress to severe forms and develop distributive shock with unknown infectious or pharmacological causes.

- The use of corticosteroids in patients with severe symptoms would be helpful for the management of the hyperinflammatory condition and control the adrenal insufficiency in these patients; however, further evidence is needed.
- The data regarding thyroid hormone alterations are consistent with evidence reported worldwide, where the alteration of TSH is a distinctive characteristic of subacute thyroiditis due to COVID-19 infection.

We are waiting for the new publications to be written on this exciting topic.

Clinical characteristics	Total	Discharge condition		p-value
		Non survivor	Survivor	
Thyroid disorder (n (%))[1/]				
Yes	39 (59,09)	18 (46,15)	21 (53,85)	0,461
No	27 (40,91)	10 (37,04)	17 (62,96)	
Adrenal alteration (n (%))[1/]				
Yes	45 (68,18)	19 (42,22)	26 (57,78)	0,961
No	21 (31,82)	9 (42,86)	12 (57,14)	
Vasoactive requirement (n (%))[1/]				
Yes	42 (63,64)	20 (47,62)	22 (52,38)	0,259
No	24 (36,36)	8 (33,33)	16 (66,67)	
Hypoglycemia (n (%))[1/]				
Yes	15 (22,73)	7 (46,67)	8 (53,33)	0,705
No	51 (77,27)	21 (41,18)	30 (58,82)	
Fever (n (%))[1/]				
Yes	16 (24,24)	5 (31,25)	11 (68,75)	0,299
No	50 (75,76)	23 (46)	27 (54)	
Days with corticosteroids (median (IQR))[2/]	9 (5-10)	7 (4-10)	10 (6-10)	0,084
Corticosteroid type (n (%))[1/]				
Dexamethasone	21 (31,82)	7 (33,33)	14 (66,67)	0,307
Methylprednisolone	45 (68,18)	21 (46,67)	24 (53,33)	
Hyperkalemia (n (%))[1/]				
Yes	7 (10,61)	3 (42,86)	4 (57,14)	1,000
No	59 (89,39)	25 (42,37)	34 (57,63)	
Sodium alteration (n (%))[1/]				
Hyponatremia	29 (43,94)	14 (48,28)	15 (51,72)	0,560
Normal	31 (46,97)	11 (35,48)	20 (64,52)	
Hypernatremia	6 (9,09)	3 (50)	3 (50)	
MV days (mediana (IQR))[2/]	8 (5-17)	9 (6-13)	8 (4-20)	0,840
Hospitalization days (median (IQR))[2/]	10 (7-19)	9 (6-13)	12 (8-30)	0,049*

Note: SD= standard deviation; IQR= interquartile range; * significance, 1/ Chi-square test, 2/ Mann Whitney test, MV: mechanical ventilation

Table 2. Clinical characteristics by discharge condition.

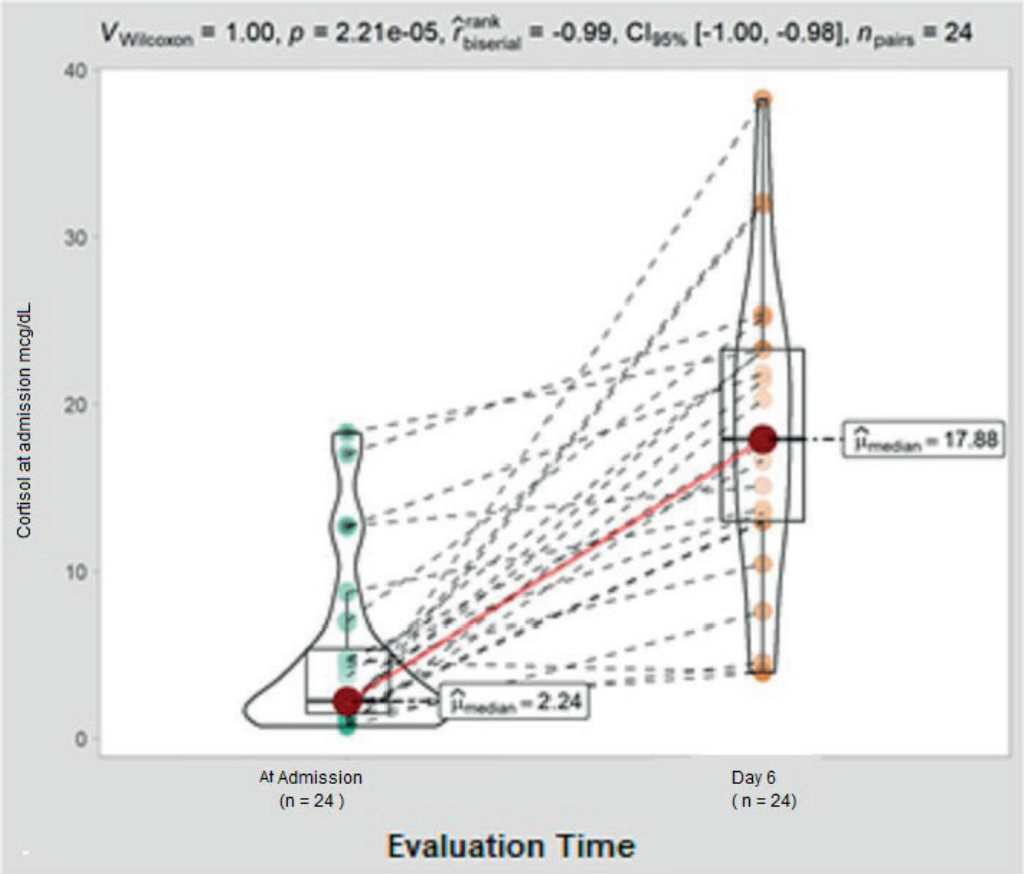

Figure 1. Comparison of cortisol at admission and six days later.

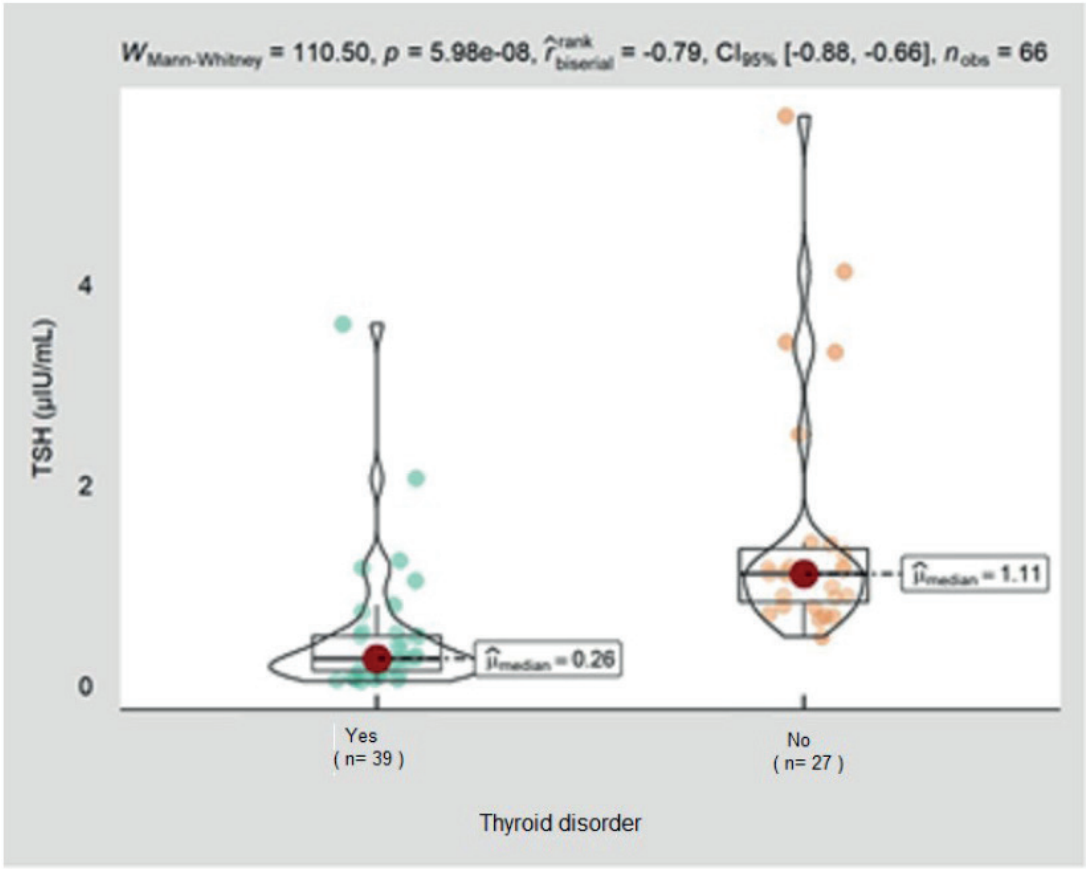

Figure 2. Comparison of TSH by presence or absence of thyroid alteration.

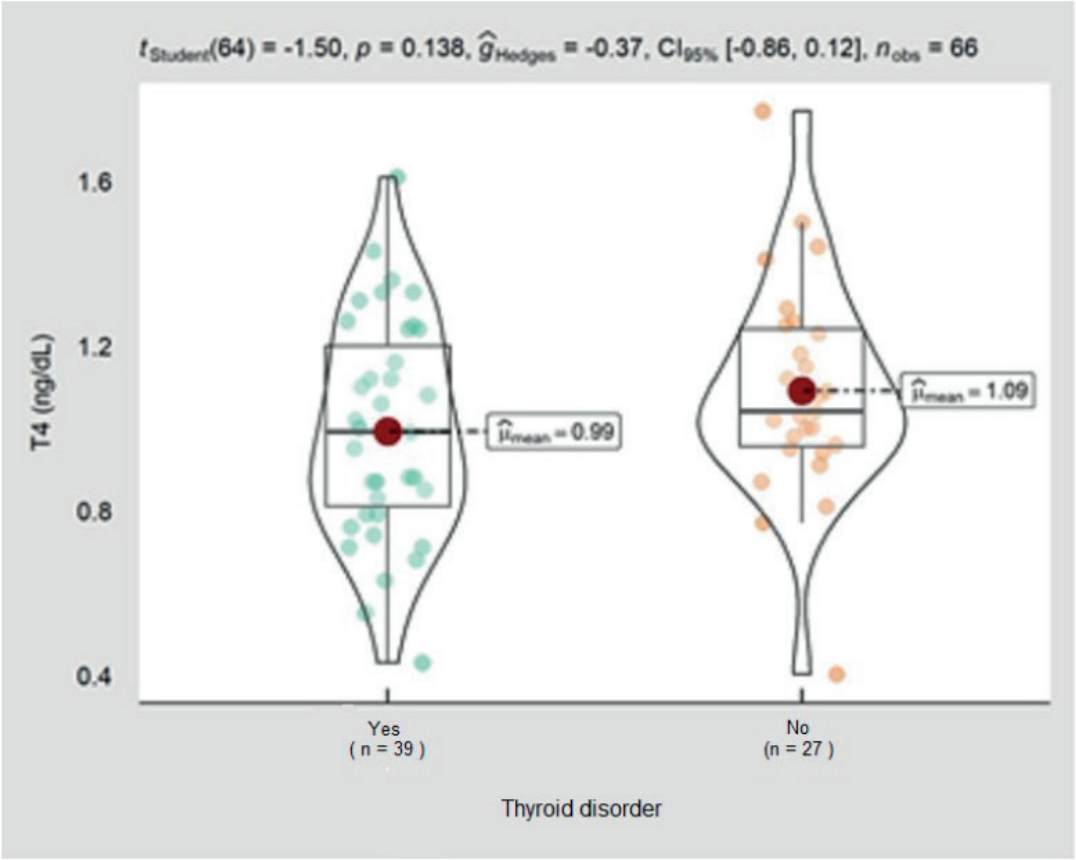

Figure 3. Comparison of T4 values in the presence or absence of thyroid alteration.

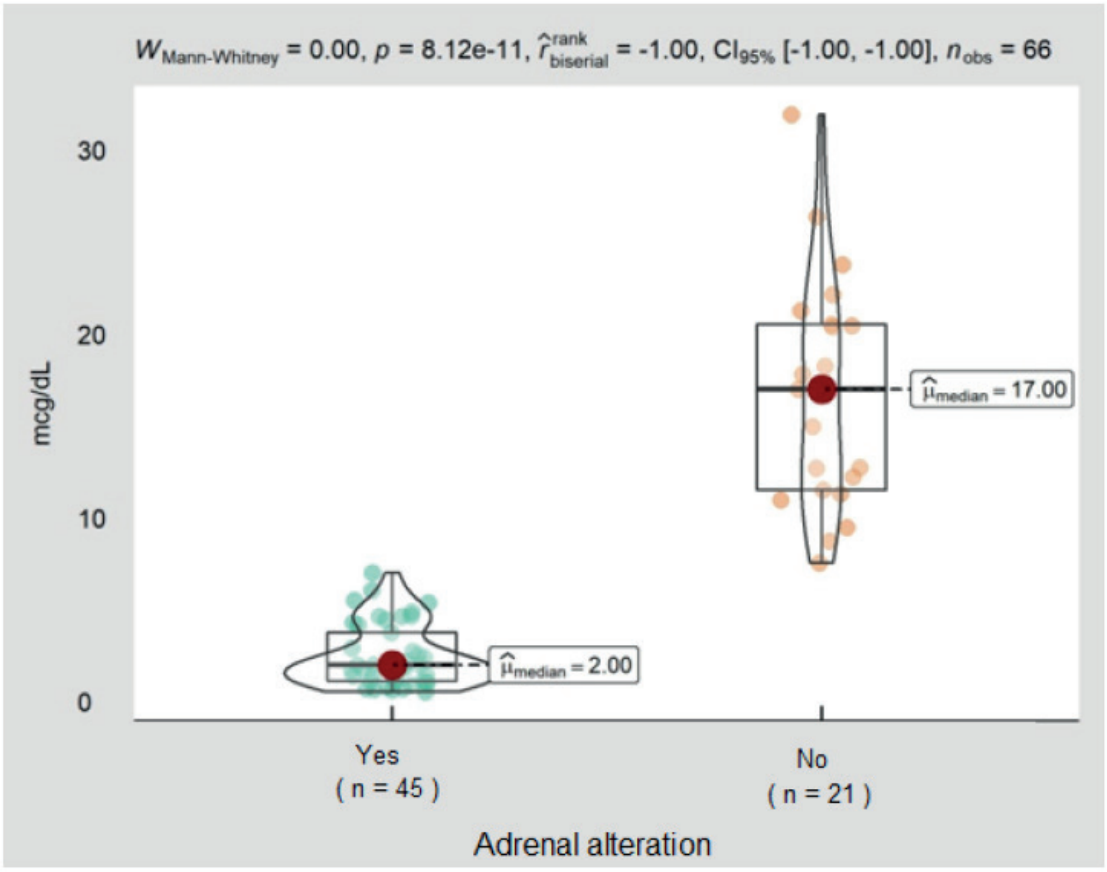

Figure 4. Comparison of cortisol values in the presence or absence of adrenal alteration.

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