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Post-COVID-19 incidentally discovered adrenal findings (a CT-focused real-life study)

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Abstract

Background: Coronavirus disease 2019 (COVID-19) pandemic was associated with unexpected endocrine findings at imaging evaluation, including adrenal incidentalomas. *Aim*: To analyze adrenal findings at computed tomography (CT) in patients who underwent an abdominal and/or thoracic CT scan for non-adrenal conditions and had a positive COVID-19 testing within six to 12 months before. *Methods*: This was a retrospective, real-life study in adults. *Results*: Two groups [group C (positive COVID-19 infection; *N*=46 patients) *vs.* group non-C (prior negative infection; *N*=74 patients)] had similar age: 57.72±14.23 *vs.* 53.74±13.90 years (p=0.134). 73.33% of patients of group C had abnormal adrenal features similar to 66.22% of patients in non-C. Prevalence of adrenal nodules (ANs) was statistically significantly higher in group C (54.35%) *vs.* non-C (33.78%) (p=0.026). Detection rate of unilateral AN (45.65% *vs.* 25.67%; p=0.029) was also higher. 41.67% of entire group (*N*=120) displayed an AN (group AN), while 58.33% were nodule-free (group non-AN), with similar age and gender distribution. The number of patients with a history of COVID-19 infection was statistically significantly higher in group AN *vs.* non-AN (50% *vs.* 30%; p=0.026). Multivariate logistic regression analysis explained 17.5% of the variance (R^2: 0.175). After adjusting for age, gender, right unilateral hyperplasia and left unilateral hyperplasia, the presence of the COVID-19 history remained statistically significantly (p=0.028) associated with increased odds of having an AN [odds ratio (OR: 2.471, 95% confidence interval (CI): 1.105–5.527]. A statistically significant correlation was found between the age and the largest diameter of AN within group AN (r=0.387, p=0.009). *Conclusions*: Awareness remains the key factor in the CT-detected lesions that have been identified after prior coronavirus infection, some being a direct consequence, while others are incidental elements.

Keywords: endocrine, coronavirus, imaging, scan, infection, CT.

Introduction

Coronavirus disease 2019 (COVID-19) infection was associated, among others, with unexpected endocrine issues, including abnormal adrenal-released cortisol levels depending on the infection severity, patient's co-morbidities and prior drug therapy exposure, while, on the other hand, numerous incidental (radiological) findings were detected in patients who underwent thoracic imaging evaluations, for instance, amid computed tomography (CT) scan [1–3]. These findings, *e.g.*, adrenal incidentalomas, were actually identified during investigations for unrelated purposes regarding a baseline (prior known) endocrine condition, but further on, they required a specific hormonal evaluation [4–6].

Most of the adrenal incidentalomas are hormonally inactive and they are generally identified in adults of 50 years or older. Typically, these masses are unusual in younger subjects and children, and, in this particular instance, a meticulous assessment is mandatory in order to exclude a malignancy, a syndromic presentation or an active endocrine ailment [7–9].

Upon the detection of an adrenal incidentaloma and its confirmation as being a non-secretor tumor, a lifelong follow-up is required according to various guidelines and protocols. One third of the non-functioning adrenal nodules (ANs) in fact display a mild cortisol (autonomous) secretion that is not correlated with the traditional clinical presentation of a Cushing's syndrome, but with distinct clusters of comorbidities, such as high blood pressure, obesity, type 2 diabetes mellitus or osteoporosis, which were reported with a higher prevalence than found in general population [10–14].

Whether COVID-19 infection represents a true pathogenic

loop in the development of the non-functioning adrenal tumors is still a matter of debate. As far as we know at this point, necrosis and transitory adrenal hyperplasia during the cytokine storm, inflammation, oxidative stress or adrenal hypoplasia caused by intensive glucocorticoids regime might explain the abnormal radiological findings in adrenal glands amid COVID-19 pandemic [15–18].

Aim

We aimed to analyze the adrenal (radiological) findings at CT scan in patients who underwent an abdominal and/or thoracic CT scan for non-adrenal conditions and had a positive COVID-19 testing within six to 12 months before.

Patients, Materials and Methods

Study design

This was a retrospective, real-life study.

Study population

Adult patients who underwent thoracic, abdominal, or thoracic-abdominal CT scans (between January 2022 and January 2023) for various (non-adrenal) conditions such as chronic respiratory or digestive conditions, kidney lesions, or non-specific abdominal pain (non-endocrine units) were included if they had a previous hospitalization within six to 12 months whereas they have been tested for COVID-19 infection.

Inclusion criteria

The following inclusion criteria were established:

▪ Adults aged of 18 years or older;

▪ Available data at current adrenal CT scan;

▪ Normal adrenal profile at hormonal testing in terms of baseline morning adrenocorticotropic hormone (ACTH), plasma morning cortisol and normal suppression during Dexamethasone suppression testing, normal plasma metanephrines and normetanephrines, biochemistry assays (blood sodium and potassium), and aldosterone-to-renin ratio;

▪ The subjects underwent a COVID-19 testing [reverse transcription polymerase chain reaction (RT-PCR) from nasopharyngeal swabs] within prior six to 12 months to the current CT exam.

Exclusion criteria

Exclusion criteria were stratified based on the following subsections:

▪ Infectious aspects:

– Acute coronavirus infection at the time of (adrenal) CT imaging;

– Severe coronavirus infection (requiring hospitalization) or diagnosis of long COVID-19 syndrome at any point in life;

– No available/clear results at RT-PCR coronavirus testing (on current admission and previous six to 12 months).

▪ General medical records and co-morbidities:

– Suspected or confirmed malignancy based on the clinical, imaging or biochemical evaluation, including a suspected lung or adrenal malignancy at CT scan;

– Corticotherapy (current or previous 12–24 months);

– Hypertension of any cause (including idiopathic).

▪ Endocrine panel:

– Prior history or current confirmation/suspicion of any adrenal pathology (*e.g.*, Cushing's syndrome, pheochromocytoma, Conn's syndrome, congenital adrenal hyperplasia, Addison disease, adrenal insufficiency, hirsutism, etc.);

– Abnormal hormonal testing at Dexamethasone suppression test or blood assays for metanephrines and normetanephrines, respectively, serum sodium, potassium, or aldosterone/renin ratio;

– Iatrogenic Cushing's syndrome;

– Clinical features caused by an adrenal condition (*e.g.*, endocrine hypertension, Cushing's syndrome-related phenotype, hirsutism, etc.);

– Patients who purposely underwent an adrenal CT scan in relationship with an endocrine (hormonal) check-up (*e.g.*, acromegaly, multiple endocrine neoplasia, Nelson's syndrome, etc.).

▪ Imaging evaluation:

– Incomplete visualization of the right/left adrenal gland at CT scan;

– Contraindication to use intravenous contrast during CT (*e.g.*, allergies, renal failure).

Study protocol

The study included 300 adults who underwent a thoracic-abdominal CT scan (with intravenous contrast) for non-adrenal ailments and the data were retrospectively analyzed as second opinion by two trained radiologists (M.C. and A.S.D.). The following categories of patients were further ruled out: the subjects with active/suspected malignancies based on the radiological and/or clinical/lab evaluation (*N*=42), the individuals with hypertension, active endocrine conditions and/or abnormal hormonal testing [including, as mentioned, baseline ACTH, plasma morning cortisol (at baseline and after Dexamethasone suppression testing), as well as plasma metanephrines and normetanephrines, serum sodium, potassium, or aldosterone/renin ratio (*N*=60)], the individuals with current acute coronavirus infection (*N*=11). Other 20 subjects were excluded because their history with regard to the COVID-19 testing within previous six to 12 months was not available/clear (*N*=20). The final study population (*N*=120) was assigned as either group C or group non-C depending on the subjects had a positive (*N*=46) or a negative (*N*=74) result at COVID-19 testing within prior six to 12 months (Figure 1).

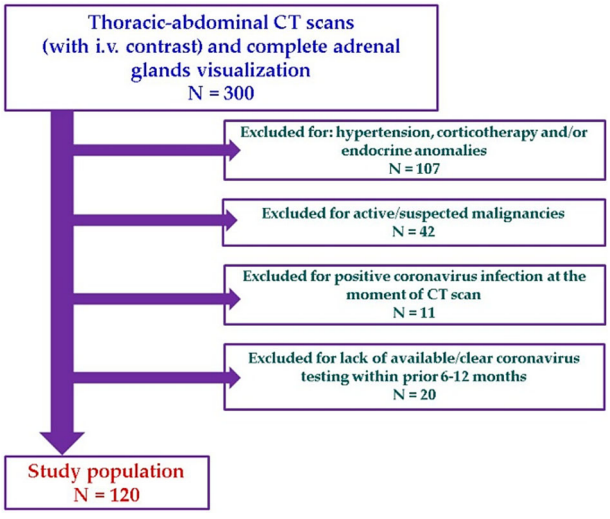

Figure 1 – ***Flow chart of the study population based on the inclusion/exclusion criteria. CT: Computed tomography; N: No. of patients.***

The data collection among the CT scan assessment included the following aspects:

▪ Adrenal glands were examined regarding their size, density and homogeneity. Incidental adrenal findings were characterized as follows: adrenal hyperplasia (defined as diffuse, smooth thickening of adrenal parenchyma without an identifiable focal mass), AN (defined as well-shaped lesion with a rounded or ovoid morphology), unilateral/bilateral presence of the lesion, location within the adrenal gland (body, medial limb, or lateral limb), and the largest diameter (cm) of the adrenal lesion. Patients with ANs suggestive for non-adenoma features were excluded [*e.g.*, cysts, myelolipomas, mixed (solid/cyst) tumors, tumors with malignant features, such as irregular margins, heterogeneous density of >10 Hounsfield Units (HU), largest diameter of >4 cm or evidence of local invasion].

▪ The investigation of the pulmonary lesions included: bronchiectasis (defined as bronchus lumen larger than the adjacent vessel), pulmonary fibrosis (interstitial septal thickening, honeycombing defined as clustered cystic air spaces predominantly in sub-pleural regions and traction bronchiectasis), the presence of a ground-glass opacity (increased attenuation without completely obscuring bronchial and vascular structures), pulmonary consolidation (increased attenuation that completely obscures bronchial and vascular structures), micronodules (<0.6 cm), nodules (>0.6 cm and ≤3 cm) and pleural thickening (pleural width of >0.3 cm). Patients with pulmonary features suggestive for a malignancy, such as the largest diameter of >3 cm, lack of intra-lesion calcifications, spiculated margins, and invasion into adjacent structures were excluded.

▪ Hepatic evaluation included measuring the cranio-caudal diameter of the right lobe (cm) and mean hepatic density (HU) and noting hepatomegaly (cranio-caudal diameter of >15.5 cm), as well as fatty liver (density of <50 HU). Focal hepatic lesions were represented by nodular calcifications (high density round lesions), cysts (fluid density round lesions with no enhancement), and hemangiomas (typical pattern of peripheral nodular enhancement). The gallbladder was examined for the presence of stones, while the history of cholecystectomy was confirmed by the detection of post-operatory clips.

▪ Spleen evaluation included the antero-posterior and cranio-caudal diameters (cm) and confirmation of splenomegaly by an antero-posterior diameter of >10.5 cm. Splenic lesions were represented by cysts (fluid density round lesions with no enhancement).

Statistical analysis

Kolmogorov–Smirnov test was used to assess the normality of data distribution. Descriptive statistics were expressed as mean ± standard deviation (SD) for normally distributed variables, and as median with interquartile range (IQR) for non-normally distributed variables. For group comparisons, the independent samples *t*-test was used when normality was met, while the Mann–Whitney *U*-test was applied for non-parametric data. Associations between categorical variables were assessed using the χ^2 (*chi*-squared) test, and Fisher's exact test when applicable. For comparisons involving more than two groups, the Kruskal–Wallis *H*-test was used. Pearson's correlation coefficient was computed to assess bivariate correlation. Binary logistic regression analysis was used to assess the relationship between a dichotomous dependent variable and multiple independent predictors. Regression coefficients (*B*) along with their standard errors (SE) were reported to quantify the effect size of each predictor. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated to express the likelihood of outcome occurrence per unit change in the independent variable. The model's explanatory power was evaluated using R^2 statistics. A cut-off *p*-value of <0.05 was statistically significant.

Ethical aspects

Ethical aspects involved the informed consent that has been signed by each patient during hospitalization (inpatient) according to each department protocol and the approval of the local Ethics Committee for retrospectively collecting the analyzed data.

Results

COVID-19 history analysis

A total of 120 patients were included in the study; 38.33% of the subjects from the entire group had a history of COVID-19 infection (group C) and 61.67% represented group non-C (*N*=74) that have been found negative at prior testing, as mentioned. The two subgroups had a similar age at CT examination: 57.72±14.23 *vs.* 53.74±13.90 years (*p*=0.134). The cohort has a mean baseline hormonal and biochemical assays, as mentioned (Tables 1 and 2).

Table 1 – ***Hormonal parameters of the study population***

Parameter	Group C (*N*=46, 38.33%)	Group non-C (*N*=74, 61.67%)	*p*-value	Normal range
Baseline blood ACTH [pg/mL], mean ± SD	14.82± 6.13	16.22± 5.42	0.751	7.2–63.3
Plasma morning cortisol [µg/dL], mean ± SD	11.20± 4.10	12.85± 3.25	0.838	4.82–19.5
Cortisol after 1 mg-Dexamethasone suppression testing [µg/dL], mean ± SD	1.05± 0.42	1.22± 0.35	0.691	<1.8
Plasma metanephrines [pg/mL], mean ± SD	61.39± 17.42	65.12± 20.35	0.414	0–100
Plasma normetanephrines [pg/mL], mean ± SD	86.52± 29.86	83.16± 35.20	0.702	0–216
Aldosterone-to-renin ratio [ng/mL//ng/mL/hour], mean ± SD	19.82± 3.03	20.15± 2.34	0.796	<30
Serum sodium [mmol/L], mean ± SD	139.40± 3.10	140.40± 4.20	0.700	136–145
Serum potassium [mmol/L], mean ± SD	3.80± 0.92	3.94± 1.01	0.654	3.5–5.1

ACTH: Adrenocorticotropic hormone; *N*: No. of patients; SD: Standard deviation.

Table 2 – ***Demographic parameters of the study population***

Parameter	Entire group (*N*=120, 100%)	Group C (*N*=46, 38.33%)	Group non-C (*N*=74, 61.67%)	*p*-value
Female, *N* (%)	89 (74.17)	32 (69.57)	57 (77.03)	
Male, *N* (%)	31 (25.83)	14 (30.43)	17 (23.97)	0.364
Age [years]				
▪ Mean ± SD	52.27± 14.10	57.72± 14.23	53.74± 13.90	0.134
▪ Median (IQR)	57.50 (44.00, 67.00)	60.00 (49.00, 69.00)	52.00 (43.00, 67.00)	
▪ Minimum, maximum	20.00, 79.00	20.00, 79.00	26.00, 79.00	

IQR: Interquartile range; *N*: No. of patients; SD: Standard deviation.

73.33% of the patients in group C had abnormal radiological features of the adrenal glands on CT, similar to 66.22% in group non-C (p=0.416). The prevalence of ANs was statistically significantly higher in group C (54.35%) *vs.* group non-C (33.78%) (p=0.026), as well as the detection rate of unilateral ANs, which was statistically significant increase in group C *vs.* group non-C (45.65% *vs.* 25.67%; p=0.029) (Table 3).

Table 3 – *Adrenal findings at CT scan*

Parameter	Entire group	Group C	Group non-C	*p*-value
Abnormal adrenal CT features, *N* (%)	82 (68.33)	33 (73.33)	49 (66.22)	0.416
Adrenal hyperplasia, *N* (%)	45 (37.50)	15 (32.61)	30 (40.54)	0.383
Unilateral hyperplasia, *N* (%)	32 (26.67)	9 (19.56)	23 (31.08)	0.165
Right hyperplasia, *N* (%)	7 (5.83)	1 (2.17)	6 (8.11)	0.266
Left hyperplasia, *N* (%)	25 (20.83)	8 (17.39)	17 (22.97)	
Bilateral hyperplasia, *N* (%)	13 (10.83)	6 (13.04)	7 (9.46)	0.539
AN, *N* (%)	50 (41.67)	25 (54.35)	25 (33.78)	0.026
Unilateral nodule, *N* (%)	40 (33.33)	21 (45.65)	19 (25.67)	0.029
Right nodule, *N* (%)	5 (4.16)	3 (6.52)	2 (2.70)	0.133
Left nodule, *N* (%)	35 (29.17)	18 (39.13)	17 (22.97)	
Adrenal body location, *N* (%)	28 (23.33)	15 (88.24)	13 (86.67)	0.991
Medial limb location, *N* (%)	2 (1.67)	1 (5.88)	1 (6.67)	
Lateral limb location, *N* (%)	2 (1.67)	1 (5.88)	1 (6.67)	
Bilateral nodules, *N* (%)	10 (8.33)	4 (8.70)	6 (8.11)	0.910
Largest diameter of AN [cm]				
▪ Mean ± SD	1.50±0.60	1.45±0.46	1.55±0.72	0.281
▪ Median (IQR)	1.36 (1.15, 1.73)	1.32 (1.14, 1.71)	1.40 (1.16, 1.75)	
▪ Minimum, maximum	0.77, 4.16	0.77, 2.56	0.80, 4.16	
Largest diameter of right AN [cm]				
▪ Mean ± SD	1.62±0.41	1.50±0.46	1.76±0.34	0.195
▪ Median (IQR)	1.50 (1.24, 1.88)	1.24 (1.17, 1.88)	1.67 (1.49, 2.03)	
▪ Minimum, maximum	1.12, 2.21	1.12, 2.11	1.48, 2.21	
Largest diameter of left AN [cm]				
▪ Mean ± SD	1.40±0.42	1.42±0.46	1.38±0.38	0.408
▪ Median (IQR)	1.32 (1.14, 1.65)	1.32 (1.08, 1.68)	1.23 (1.16, 1.54)	
▪ Minimum, maximum	0.77, 2.56	0.77, 2.56	0.95, 2.30	

AN: Adrenal nodule; CT: Computed tomography; IQR: Interquartile range; *N*: No. of patients; SD: Standard deviation.

There was no statistically significant difference between groups regarding the location of unilateral nodules on the right or left adrenal gland, neither on the body, medial limb or lateral limb of the adrenal gland. The largest diameter of the ANs was similar in group C and group non-C (1.45±0.46 *vs.* 1.55±0.72 cm; p=0.281) (Figure 2).

Bronchiectasis was statistically significant more frequently in group C *vs.* group non-C (92.86% *vs.* 67.57%; p=0.002). Ground-glass opacity was statistically significant and more common in group C *vs.* group non-C (32.56% *vs.* 9.46%; p=0.002) (Table 4).

Interestingly, 20.00% of the patients from group C had a history of cholecystectomy *vs.* 6.76% in group non-C (p=0.034) (Table 5).

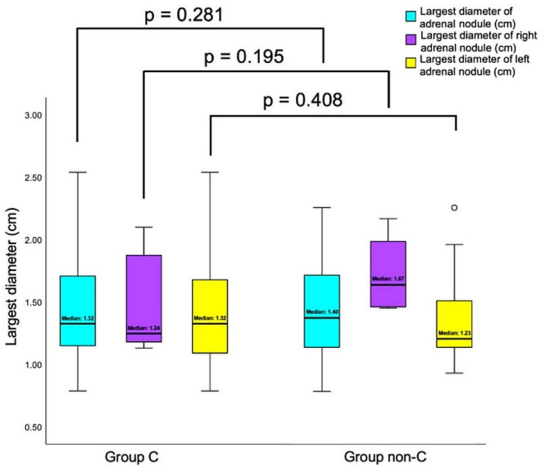

Figure 2 – *Boxplots showing the median for the largest diameter of the AN, of the right AN, and, respectively, of the left AN. AN: Adrenal nodule.*

Table 4 – *Pulmonary radiological features at CT scan in the entire group (N=120), group C (N=46), and group non-C (N=74)*

Parameter	Entire group	Group C	Group non-C	*p*-value
Pulmonary lesions, *N* (%)	108 (90.00)	42 (97.67)	66 (89.19)	0.097
Bronchiectasis, *N* (%)	89 (74.16)	39 (92.86)	50 (67.57)	*0.002*
Pulmonary fibrosis, *N* (%)	63 (52.50)	23 (53.49)	40 (54.05)	0.953
Ground-glass opacity, *N* (%)	21 (17.50)	14 (32.56)	7 (9.46)	*0.002*
Pulmonary consolidation, *N* (%)	5 (4.17)	2 (4.65)	3 (4.05)	0.878
Pulmonary micronodules, *N* (%)	37 (30.83)	14 (33.33)	23 (31.08)	0.802
Pulmonary nodules, *N* (%)	15 (12.50)	5 (11.63)	10 (13.51)	0.769
Pleural thickening, *N* (%)	18 (15.00)	7 (16.28)	12 (16.22)	0.871

CT: Computed tomography; *N*: No. of patients.

Table 5 – *Hepatic and splenic CT parameters of the study population*

Parameter	Entire group (*N*=120, 100%)	Group C (*N*=46, 38.33%)	Group non-C (*N*=74, 61.67%)	*p*-value
Right hepatic lobe cranio-caudal diameter [cm]				
▪ Mean ± SD	15.57±1.47	15.65±1.62	15.50±1.36	0.748
▪ Median (IQR)	15.50 (14.49, 16.51)	15.61 (14.56, 16.63)	15.04 (14.46, 16.39)	
▪ Minimum, maximum	12.67, 18.94	12.67, 18.94	13.22, 17.84	
Hepatic parenchyma density [HU]				
▪ Mean ± SD	45.53±1.47	43.34±17.67	46.83±11.47	0.249
▪ Median (IQR)	49.00 (37.00, 55.00)	52.00 (28.00, 57.00)	49.00 (41.50, 54.00)	
▪ Minimum, maximum	2.00, 66.00	2.00, 65.00	7.00, 66.00	

Parameter	Entire group (*N*=120, 100%)	Group C (*N*=46, 38.33%)	Group non-C (*N*=74, 61.67%)	*p*-value
Hepatomegaly, *N* (%)	40 (80.00)	21 (77.78)	19 (82.61)	0.670
Fatty liver, *N* (%)	41 (34.17)	16 (40.00%)	25 (34.25)	0.543
Focal hepatic lesions, *N* (%)	30 (25.00)	14(31.82)	16 (21.62)	0.219
Hepatic calcifications, *N* (%)	12 (10.00)	4 (9.52)	8 (10.81)	0.827
Hepatic cyst, *N* (%)	14 (11.67)	7 (16.28)	7 (9.46)	0.273
Hepatic hemangioma, *N* (%)	3 (2.50)	2 (4.76)	1 (1.35)	0.297
Gallbladder stones, *N* (%)	7 (5.83)	4 (10.00)	3 (4.05)	0.238
CHE, *N* (%)	13 (10.83)	8 (20.00)	5 (6.76)	*0.034*
Splenic antero-posterior diameter [cm]				
▪ Mean ± SD	9.57±1.64	9.79±1.70	9.44±1.61	0.324
▪ Median (IQR)	9.49 (8.44, 10.57)	9.88 (8.99, 10.84)	9.25 (8.43, 10.35)	
▪ Minimum, maximum	6.28, 16.04	6.28, 13.07	6.66, 16.04	
Splenic cranio-caudal diameter [cm]				
▪ Mean ± SD	10.01±1.30	9.72±1.87	10.21±1.34	0.092
▪ Median (IQR)	10.10 (9.20, 10.81)	9.81 (9.03, 10.56)	10.15 (9.47, 10.93)	
▪ Minimum, maximum	6.80, 13.40	6.80, 11.59	7.00, 13.40	
Splenomegaly, *N* (%)	23 (19.17)	7 (17.07)	16 (21.62)	0.559
Focal splenic lesions, *N* (%)	1 (0.83)	0 (0.00)	1 (1.35)	0.999
Splenic cyst, *N* (%)	1 (0.83)	0 (0.00)	1 (1.35)	0.999

CHE: Cholecystectomy; CT: Computed tomography; HU: Hounsfield Units; IQR: Interquartile range; *N*: No. of patients; SD: Standard deviation.

Multivariate logistic regression showed that subjects with an AN were two times more likely to have a history of COVID-19 (OR: 2.507, 95% CI: 1.034–6.074, *p*=0.042), while subjects confirmed with bronchiectasis were six times more likely to have a history of COVID-19 (OR: 6.755, 95% CI 1.635–27.911, *p*=0.008) after adjusting for age, cholecystectomy, and ground-glass opacity (Table 6).

Table 6 – ***Multivariate logistic regression regarding COVID-19 history***

	B	SE	*p*-value	OR (95% CI)
Parameter	-3.394	1.182	0.004	0.034
Age	0.007	0.017	0.686	1.007 (0.973–1.042)
Adrenal nodule	0.919	0.452	*0.042*	2.507 (1.034–6.074)
Cholecystectomy	0.847	0.716	0.236	2.334 (0.574–9.491)
Bronchiectasis	1.910	0.724	*0.008*	6.755 (1.635–27.911)
Ground-glass opacity	1.157	0.636	0.069	3.179 (0.913–11.065)
	R^2: 0.257			

B: Unstandardized coefficient; CI: Confidence interval; COVID-19: Coronavirus disease 2019; OR: Odds ratio; R^2: Multiple correlation coefficient; SE: Standard error.

The other parameters were not statistically significantly associated with a history of COVID-19 in the multivariate model. The model explained 25.7% of the variance (R^2: 0.257) (Figure 3).

The population was divided into six age groups, and the rate of COVID-19 history was calculated for each group. There was no statistically significant association between the age group and the history of COVID-19 infection (*p*=0.622) (Table 7).

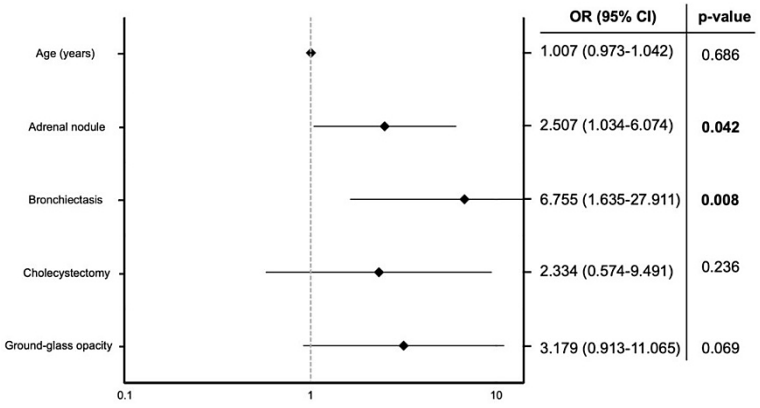

Figure 3 – ***Forest plot showing the OR for COVID-19 history (N=120). COVID-19: Coronavirus disease 2019; OR: Odds ratio.***

Table 7 – ***Age group analysis***

Age group [years]	Entire group, *N* (%)	Group C, *N* (%)	Group non-C, *N* (%)	*p*-value
20–29	6 (5.00)	3 (6.52)	3 (4.05)	0.622
30–39	11 (9.17)	2 (4.35)	9 (12.16)	
40–49	28 (23.33)	9 (19.57)	19 (25.68)	
50–59	22 (18.33)	9 (19.57)	13 (17.57)	
60–69	32 (26.67)	13 (28.26)	19 (25.68)	
70–79	21 (17.50)	10 (21.74)	11 (14.86)	

N: No. of patients.

Analysis of the incidental adrenal nodules at CT scan

41.67% of the entire group (*N*=120) displayed an AN (group AN), while 53 subjects (representing 58.33% of the entire group) were nodule-free at CT scan (group non-AN). Age and gender distribution was similar between the group AN and non-AN. The number of patients with a history of COVID-19 infection was statistically significantly higher in group AN *vs.* group non-AN (50% *vs.* 30%; *p*=0.026) (Table 8).

Table 8 – *Demographic parameters of patients in group AN (N=50) and group non-AN (N=70)*

Parameter	Group AN	Group non-AN	*p*-value
Females, *N* (%)	36 (72.00)	53 (75.71)	
Males, *N* (%)	14 (28.00)	17 (24.29)	0.647
COVID-19 history, *N* (%)	25 (50.00)	21 (30.00)	*0.026*
Age [years]			
▪ Mean ± SD	57.16±14.43	53.91±13.81	0.215
▪ Median (IQR)	62.00 (48.00, 68.00)	55.00 (43.00, 65.00)	
▪ Minimum, maximum	22.00, 79.00	20.00, 79.00	

AN: Adrenal nodule; IQR: Interquartile range; *N*: No. of patients; SD: Standard deviation.

Unilateral hyperplasia was found in 18.00% of the subjects from group AN and 32.86% of group non-AN, respectively (p=0.070). Of these, group AN had statistically significantly more patients with right adrenal hyperplasia (10.00%) *vs.* group non-AN (2.86%) and statistically significant less patients with left adrenal hyperplasia (8.00% *vs.* 30.00%) (p=0.006) (Table 9).

Table 9 – *Adrenal radiological features at CT scan in group AN*

Parameter	Group AN	Group non-AN	*p*-value
Adrenal hyperplasia, *N* (%)	13 (26.00)	32 (45.71)	*0.028*
Unilateral hyperplasia, *N* (%)	9 (18.00)	23 (32.86)	0.070
Right hyperplasia, *N* (%)	5 (10.00)	2 (2.86)	*0.006*
Left hyperplasia, *N* (%)	4 (8.00)	21 (30.00)	
Bilateral hyperplasia, *N* (%)	4 (8.00)	9 (12.86)	0.399

AN: Adrenal nodule; CT: Computed tomography; IQR: Interquartile range; *N*: No. of patients; SD: Standard deviation.

The rate of pulmonary lesions was similar between group AN and group non-AN (Table 10).

Table 10 – *Pulmonary radiological aspects in the group AN (N=50) and group non-AN (N=70)*

Parameter	Group AN	Group non-AN	*p*-value
Pulmonary lesions, *N* (%)	45 (93.75)	63 (91.30)	0.625
Bronchiectasis, *N* (%)	38 (79.17)	51 (75.00)	0.601
Pulmonary fibrosis, *N* (%)	27 (56.25)	36 (52.17)	0.664
Ground-glass opacity, *N* (%)	12 (25.00)	9 (13.04)	0.097
Pulmonary consolidation, *N* (%)	2 (4.17)	3 (4.35)	0.962
Pulmonary micronodules, *N* (%)	17 (36.17)	20 (28.99)	0.415
Pulmonary nodules, *N* (%)	6 (12.50)	9 (13.04)	0.931
Pleural thickening, *N* (%)	9 (18.75)	10 (14.49)	0.539

AN: Adrenal nodule; *N*: No. of patients.

Hepatic and splenic parameters were similar between group AN and group non-AN (Table 11).

Table 11 – *Hepatic and splenic CT parameters of patients in group AN (N=50, 41.67%) and group non-AN (N=70, 58.33%)*

Parameter	Group AN	Group non-AN	*p*-value
Right hepatic lobe cranio-caudal diameter [cm]			
▪ Mean ± SD	15.59±1.52	15.55±1.45	0.931
▪ Median (IQR)	15.59 (14.51, 16.49)	15.04 (14.49, 16.51)	
▪ Minimum, maximum	12.67, 18.94	13.22, 18.53	
Hepatic parenchyma density [HU]			
▪ Mean ± SD	45.59±15.57	45.59±13.01	0.974
▪ Median (IQR)	48.00 (40.00, 56.00)	49.00 (37.00, 54.00)	
▪ Minimum, maximum	2.00, 66.00	7.00, 63.00	
Hepatomegaly, *N* (%)	22 (78.57)	18 (81.82)	0.776
Fatty liver, *N* (%)	19 (28.78)	22 (34.38)	0.630
Focal hepatic lesions, *N* (%)	15 (30.00)	15 (22.06)	0.328
Hepatic calcifications, *N* (%)	6 (12.00)	6 (9.09)	0.610
Hepatic cyst, *N* (%)	7 (14.00)	7 (10.45)	0.558
Hepatic hemangioma, *N* (%)	1 (2.04)	2 (2.99)	0.752
Hepatic mass, *N* (%)	4 (8.00)	3 (4.41)	0.455
Gallbladder stones, *N* (%)	3 (6.12)	4 (6.15)	0.994
Cholecystectomy, *N* (%)	7 (14.29)	6 (9.23)	0.401
Splenic antero-posterior diameter [cm]			
▪ Mean ± SD	9.62±1.39	9.53±1.83	0.787
▪ Median (IQR)	9.75 (9.50, 10.81)	9.25 (8.45, 10.32)	
▪ Minimum, maximum	6.28, 11.88	6.63, 16.04	
Splenic cranio-caudal diameter [cm]			
▪ Mean ± SD	9.93±1.35	10.09±1.26	0.561
▪ Median (IQR)	10.04 (9.16, 10.63)	10.13 (9.28, 10.85)	
▪ Minimum, maximum	6.80, 13.09	7.00, 13.40	
Splenomegaly, *N* (%)	8 (16.33)	15 (22.73)	0.396
Focal splenic lesions, *N* (%)	0 (0.00)	1 (1.52)	0.999
Splenic cyst, *N* (%)	0 (0.00)	1 (1.52)	0.999

AN: Adrenal nodule; CT: Computed tomography; HU: Hounsfield Units; IQR: Interquartile range; *N*: No. of patients; SD: Standard deviation.

Multivariate logistic regression analysis was performed to identify factors associated with the confirmation of ANs. The model explained 17.5% of the variance (R^2: 0.175). After adjusting for age, gender, right unilateral hyperplasia and left unilateral hyperplasia, the presence of the COVID-19 history remained statistically significantly (p=0.028) associated with increased odds of having an AN (OR: 2.471, 95% CI: 1.105–5.527) (Table 12).

Table 12 – *Multivariate logistic regression for predicting the diagnosis of an adrenal nodule*

	B	SE	*p*-value	OR (95% CI)
Parameter	-1.038	0.954	0.276	0.354
Age	0.009	0.014	0.552	1.009 (0.980–1.038)
Gender	0.046	0.453	0.920	1.047 (0.431–2.541)
COVID-19 history	0.905	0.411	*0.028*	2.471 (1.105–5.527)
Right unilateral hyperplasia	1.324	0.881	0.133	3.759 (0.668–21.142)
Left unilateral hyperplasia	-1.462	0.599	*0.015*	0.232 (0.072–0.750)
	R^2: 0.175			

B: Unstandardized coefficient; CI: Confidence interval; COVID-19: Coronavirus disease 2019; OR: Odds ratio; R^2: Multiple correlation coefficient; SE: Standard error.

Left unilateral adrenal hyperplasia was statistically significantly (p=0.015) associated with a decreased likelihood of having an AN (OR: 0.232, 95% CI: 0.072–0.750). Age, gender and right unilateral hyperplasia were not statistically significantly associated with an AN confirmation after adjustment (Figure 4).

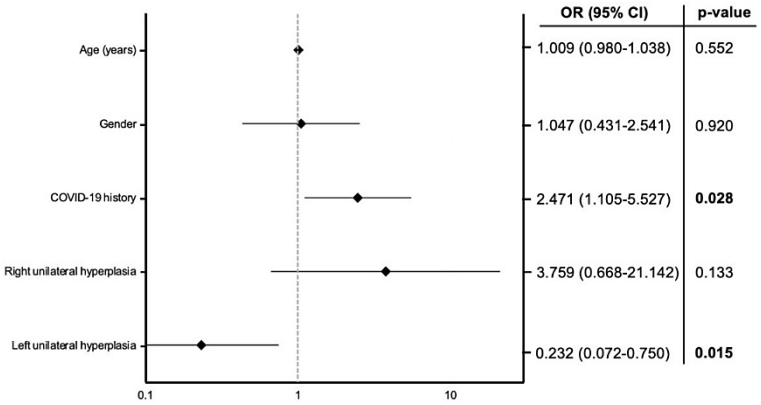

Figure 4 – ***Forest plot showing odds ratio for the diagnosis of adrenal nodule.***

Analysis of the subgroup of patients diagnosed with an adrenal nodule at CT scan (adrenal incidentalomas)

A statistically significant, positive correlation was found between the age and the largest diameter of AN within group AN (r=0.387, p=0.009) (Figure 5).

Age was statistically significantly negatively correlated with the splenic antero-posterior diameter (r=-0.406, p=0.007). Splenic cranio-caudal diameter was positively correlated with the hepatic cranio-caudal diameter (r=0.609, p=0.003), and negatively with the hepatic mean density (r=-0.434, p=0.015) (Table 13).

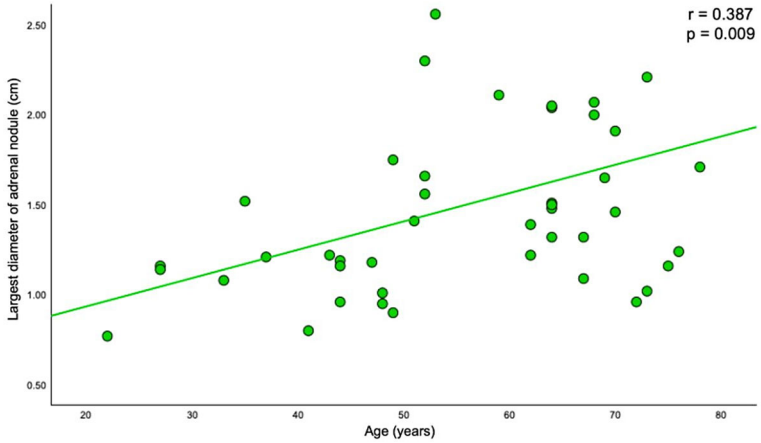

Figure 5 – ***Scatterplot showing the positive correlation between the age and the largest diameter of adrenal nodule in group AN (N=50).***

Table 13 – ***Correlations between the age, the largest diameter of detected AN, hepatic and splenic diameters in group AN (N=50)***

Parameter	Age [years]	Largest diameter [cm]	Hepatic cranio-caudal diameter [cm]	Hepatic mean density [HU]	Splenic antero-posterior diameter [cm]	Splenic cranio-caudal diameter [cm]
Age [years]		*r=0.387* *p=0.009*	r=0.151 p=0.492	r=-0.061 p=0.707	*r=-0.406* *p=0.007*	r=0.010 p=0.952
Largest diameter [cm]	*r=0.387* *p=0.009*		r=0.177 p=0.468	r=-0.110 p=0.521	r=-0.050 p=0.770	r=0.074 p=0.671
Hepatic cranio-caudal diameter [cm]	r=0.151 p=0.492	r=0.177 p=0.468		r=-0.325 p=0.162	r=0.080 p=0.745	*r=0.609* *p=0.003*
Hepatic mean density [HU]	r=-0.061 p=0.707	r=-0.110 p=0.521	r=-0.325 p=0.162		r=-0.138 p=0.416	*r=-0.434* *p=0.015*
Splenic antero-posterior diameter [cm]	*r=-0.406* *p=0.007*	r=-0.050 p=0.770	r=0.080 p=0.745	r=-0.138 p=0.416		r=0.115 p=0.516
Splenic cranio-caudal diameter [cm]	r=0.010 p=0.952	r=0.074 p=0.671	*r=0.609* *p=0.003*	*r=-0.434* *p=0.015*	r=0.115 p=0.516	

AN: Adrenal nodule; HU: Hounsfield Units; *N*: No. of patients.

The largest diameter of the newly detected AN was statistically significantly different among the age groups (p=0.002) (Table 14).

The highest diameter (1.93±0.46 cm) of the adrenal incidentalomas was found in the 50–59 years age group (Figure 6).

There was no statistically significant association between age groups and the identification of an AN (Table 15).

No association between the age group and AN was found in the entire group (p=0.696), nor in group C (p=0.681) or group non-C (p=0.935) (Figure 7).

Table 14 – ***The largest diameter of the adrenal nodule in each age group***

Age group [years]	Largest diameter of adrenal nodule [cm], mean ± SD	*p*-value
20–29	1.02±0.22	*0.002*
30–39	1.27±0.23	
40–49	1.11±0.27	
50–59	1.93±0.46	
60–69	1.59±0.34	
70–79	1.76±0.99	

SD: Standard deviation.

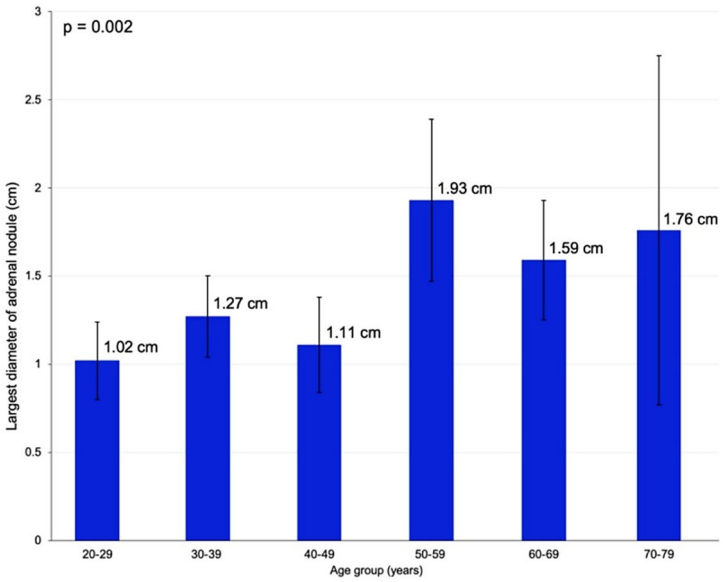

Figure 6 – ***Bar chart showing mean largest diameter of adrenal nodule in each age group (N=120).***

Table 15 – ***Percent of patients with COVID-19 history and AN by age groups (N=120)***

Age group [years]	*N* (%)	AN in entire group (*N*=50, 41.67%)	AN in group C (*N*=25, 20.83%)	AN in group non-C (*N*=25, 20.83%)
20–29	6 (5.00)	3 (6.00)	2 (8.00)	1 (4.00)
30–39	11 (9.17)	3 (6.00)	1 (4.00)	2 (8.00)
40–49	28 (23.33)	10 (20.00)	3 (12.00)	7 (28.00)
50–59	22 (18.33)	8 (16.00)	4 (16.00)	4 (16.00)
60–69	32 (26.67)	15 (30.00)	9 (36.00)	6 (24.00)
70–79	21 (17.50)	11 (22.00)	6 (24.00)	5 (20.00)
		p=0.696	*p*=0.681	*p*=0.935

AN: Adrenal nodule; COVID-19: Coronavirus disease 2019; *N*: No. of patients.

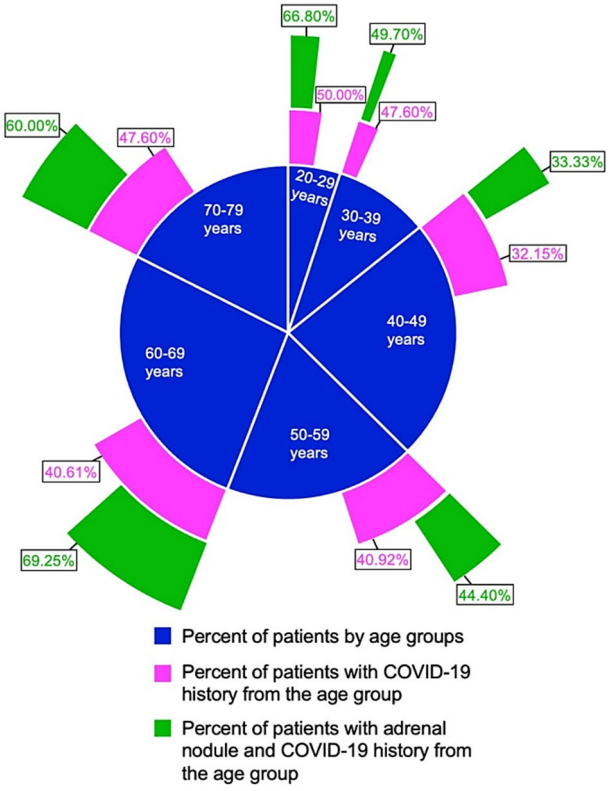

Figure 7 – ***Multi-level doughnut chart showing the percent of patients with COVID-19 history and adrenal nodule by age-group.***

Discussions

Amid this real-life study, 120 patients met the entire board of inclusion and stratified exclusion criteria (upon a clinical, radiological and hormonal perspective) and were analyzed after considering a positive (38.33%) or negative (61.67%) at COVID-19 testing up to one year prior to the current hospitalization. These two groups had a similar age at the moment of CT scan (a median of 60 *vs.* 52 years in group C *vs.* group non-C), and a similar rate of incidental radiological findings (73.33% *vs.* 66.22%) according to the elements that have been taken into consideration across the protocol of assessments.

However, the prevalence of ANs (tumors that may be regarded as true endocrine incidentalomas under these distinct circumstances) increased in group C *vs.* group non-C (54.35% *vs.* 33.78%, *p*=0.026), as well as the rate of unilateral nodules (45.66% *vs.* 25.67%, *p*=0.029). The largest diameter was statistically significantly different across the age groups (*p*=0.002). Overall, prior coronavirus infection might raise the issue of a potential pathogenic connection with an AN, which remains an open issue nowadays [17–19], and it was out of the scope of this clinical real-life setting to determine the molecular and histological insights that connect the adrenal anomalies with the viral infection itself.

Endocrine incidentalomas: radiological and hormonal interplay

After adjusting for age, gender, unilateral hyperplasia, and the COVID-19 history remained statistically significantly associated with increased odds of having the diagnosis of an AN (*p*=0.028). The identification of an adrenal incidentaloma across thoracic-abdominal CT scans during COVID-19 pandemic was analyzed by several studies. For instance, we mention the study of Chen *et al.* [1] that has been published in 2024 in 121 patients who underwent adrenal surgery for non-functional adrenal incidentalomas with/without a history of COVID-19 infection, and this retrospective cohort included subjects who were hospitalized between April 2022 and June 2023. The clinical manifestations of the AN were similar between the patients with *vs.* without a previous coronavirus infection, suggesting that COVID-19

might not affect the endocrine picture in this specific instance [1]. Of note, in this study, we only included tumors with non-functional hormonal profile in subjects to whom (additionally) an active malignancy was ruled out based on the clinical and radiological evaluation (Figure 8).

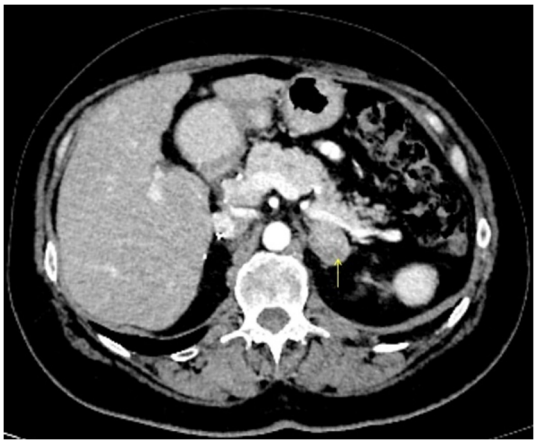

Figure 8 – ***Left adrenal tumor with non-functioning profile in a menopausal adult (CT scan).***

Generally, 5% to 30% of the non-functioning adrenal tumors might display a mild autonomous cortisol secretion, which is detected, not by baseline ACTH and cortisol assays, but by post-Dexamethasone cortisol level (above 1.8 μg/dL and below 5 μg/dL) in the absence of a traditional phenotype for Cushing's syndrome [4, 20–25]. In this study, we excluded the patients that showed even a small hormonal activity in order to eliminate the bias that comes from the dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis and its reflection into morphological gland aspects. For example, Martin *et al.* [4] showed in a retrospective pre-pandemic study that 71.95% of the consecutive cases of adrenal tumors (N=474; median age of 56 years, 81.06% were females) are non-functional, while 5.31% of the tumors showed a mild autonomous cortisol secretion [4].

Moreover, patients with mild autonomous cortisol excess have a higher risk of cardio-metabolic and osseous complications than found in unselected populations [26–28]. Other endocrine tumors such as Conn's tumor and pheochromocytoma might be incidentally detected, as well, and associate various cardio-metabolic issues [29–31]. In this cohort, we tested the adrenal hormones panel and excluded any hypertensive individual in order to reduce this type of endocrine bias.

Non-adrenal findings

One third, respectively, two thirds of the study patients displayed non-adrenal findings upon CT scan at hepatic-splenic level (depending on the subgroup), and overall, more than half had overlapping lung lesions. COVID-19 pandemic associated an increased detection rate of incidental lung nodules underlying malignant features that otherwise might undergo completely asymptomatic for years, but in this study, we excluded any suspected pulmonary cancer [32–35]. Moreover, thoracic and even cardiac incidentalomas might be detected at imaging screening, as well [36–38], as similarly mentioned for the endocrine glands, noting that the most frequent endocrine incidentaloma in the general population is actually a thyroid nodule (affecting 5% to 20% of different subgroups) [39–41]. We found that bronchiectasis was statistically significant more frequently in group C *vs.* group non-C (92.86% *vs.* 67.57%; p=0.002), and subjects confirmed with bronchiectasis were six times more likely to have a history of COVID-19. A potential pathogenic connection with the prior viral infection may be suspected, yet of indeterminate significance at this point [42, 43].

Coronavirus infection and adrenal anomalies: from accidental detection of incidentalomas to a pathogenic involvement

The rate of patients with a history of COVID-19 infection was statistically significantly increased in the subgroup of patients confirmed with an adrenal incidentaloma/nodule (50%) *vs.* the subgroup without this lesion (30%; p=0.026). This difference in the viral infection prevalence does not necessarily imply a pathogenic role of the virus. However, angiotensin-converting enzyme-2 receptor which helps the entrance of the coronavirus into human cells is widely expressed in the endocrine glands, including adrenal, thyroid and pituitary, and secondary hormonal anomalies have been reported in the infected population, both in adult and pediatric patients without a prior history of any endocrine disease. Reimondo *et al.* [44] showed in one study published in 2024 (N=402 subjects who were admitted as emergency caused by a coronavirus infection) that 24.9% of them had anomalies of the adrenal morphology, namely, 15.4% had adrenal hyperplasia, and 9.5% associated ANs. Multivariate regression found that adrenal hyperplasia was an independent risk factor for a fatal outcome, as similarly observed for older age and the co-presence of an active cancer [45].

Notably, the virus might cause adrenal infarction, hemorrhage, and direct tissue injury, thrombosis of the adrenal veins since the glands are highly vascularized and this becomes a vulnerable aspect in front of an endothelial virus- or immune-mediated attack. Moreover, under the large virus-related spectrum of autoimmune anomalies, antibodies against adrenals might develop (autoimmune adrenalitis), which further initiates an adrenal failure or complicates a prior adrenal insufficiency [46]. Critical illness-related corticosteroid insufficiency represented another type of adrenal involvement [44]. Moreover, glucocorticoids administration during severe coronavirus infection further contributed to the dysfunction of HPA axis [47, 48].

Limitations and further research

As limits of the study, we mention the sample size amid a retrospective design, noting that we only included the patients with baseline normal adrenal testing in terms of blood morning ACTH, cortisol, metanephrines and normetanephrines, as well as normal response to a low-Dexamethasone test aldosterone-to-renin ratio and blood sodium/potassium. Also, the exclusion of hypertensive patients reduced the cohort size, and this was meant to avoid the bias of potential co-presence of adrenal anomalies in individuals with high blood pressure (noting an age-dependent increasing incidence of ANs in older hypertensive seniors). Long-term follow-up might show a distinction between transitory and permanent radiological findings and reveal the size changes of the ANs. Further understanding of the pathogenic mechanisms relating coronavirus infection to the adrenal (radiological/morphological) anomalies is needed

starting from experimental models upon this type of clinical observations. Also, we did not take into consideration the influence of vaccination against coronavirus. A few data suggested that in apparently healthy individuals, a potential link in identifying adrenal hyperplasia or even hemorrhage after vaccination, while in those with prior adrenal insufficiency an adrenal crisis might be triggered [49–52]. No histological confirmation was performed since the patients were not surgery candidates. Also, other authors suggested that cytokine storm-related cortisol release causing ACTH-independent pseudo-Cushing syndrome might come with long-term morphological consequences of the adrenal glands, which might explain the incidentalomas, or with chronic adrenal hypofunction in some glands' areas, even after recovery [53–56]. On the other hand, other hypothesis suggested that prior adrenal incidentalomas to infection might have impaired the disease outcome, as similarly found in the outcome of other endocrine and non-endocrine ailments [57–66]. These are yet to be explored.

Conclusions

Awareness remains the key factor in the CT-detected lesions that have been identified after prior coronavirus infection, some being a direct consequence, while others are incidental elements. This increases the overall disease burden and many post-pandemic lessons are still to be learnt. According to the current study, the prevalence of ANs in previously positive patients is more than 50% and 33% in those who were negative at RT-PCR. We found some interesting associations between the age group and the history of COVID-19 infection. The rate of patients with a history of COVID-19 infection was higher in the subgroup with incidentalomas, while identifying the pathogenic role of the infection in this masses development is still an open matter.

Conflict of interests

The authors declare no conflict of interests.

Institutional Review Board Statement

The Ethics Committee of Scientific Research of Carol Davila University of Medicine and Pharmacy, Bucharest, Romania approved this study (No. 29336 from 17 October 2025).

Informed Consent Statement

Patient consent was waived due to retrospective design.

Data Availability Statement

No other data are available.

Acknowledgments

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