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COVID-19 AND PITUITARY DISEASES

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DISCLOSURES

Conflict of interest

Consultant for Abiogen, Astellas, Ipsen, Novo Nordisk, Pfizer, Recordati, Shire/Takeda

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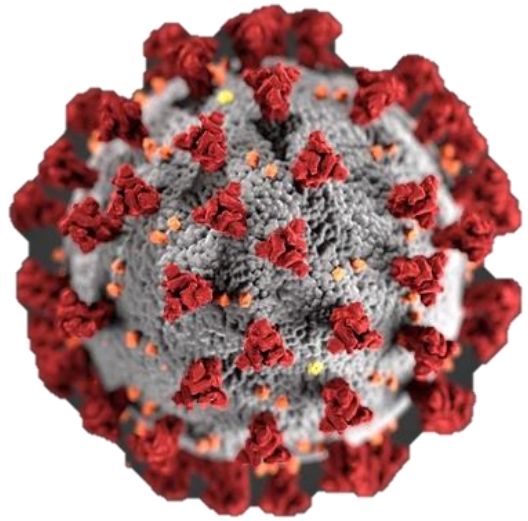
AGENDA

- COVID-19: epidemiology and main endocrine manifestations
- COVID-19 and the pituitary
- COVID-19 and pituitary adenomas
- COVID-19 and hypopituitarism
- COVID-19 vaccination and pituitary diseases

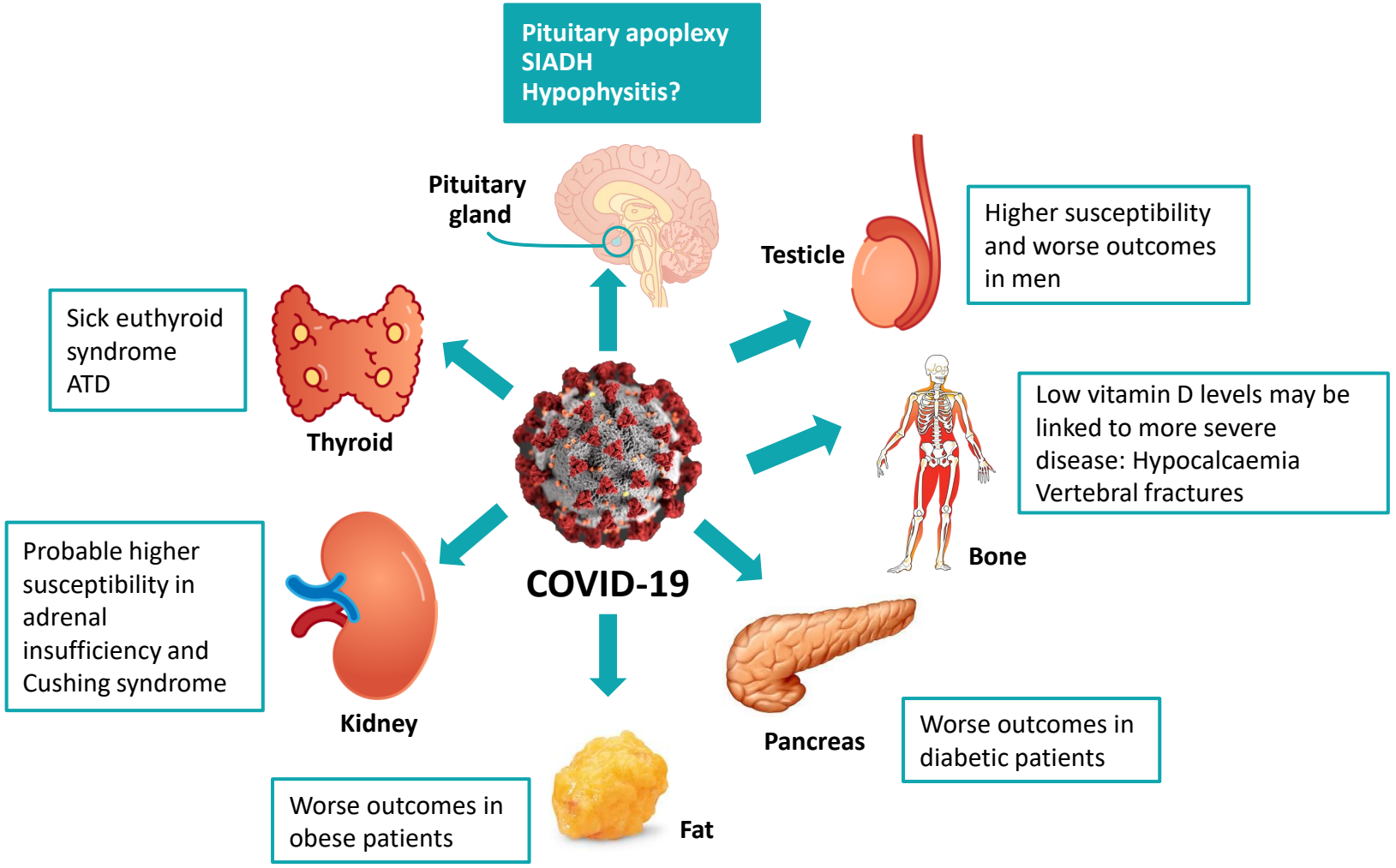


COVID-19: THE ITALIAN NUMBERS

- In Italy, as of (24 August 2021)
- **4,500,000** confirmed cases of COVID-19 (slightly more than 2% of **213,00,000** cases worldwide)
- **129,000 deaths (3**% of total deaths reported worldwide so far – 4,440,000) i.e. more than 3 times than expected based on the population (**18th in the world** per million population)
- Mean age of patients who died: 80 years (20 years more than the median age of infected patients; < 1% under 50 years of age; the vast majority were over 70 years of age)
- Mean number of comorbidities (i.e. obesity, diabetes, hypertension, cardiovascular diseases) in these patients: 3.4 (median ± SD: 3 ± 2.0); **62.6%** presented **≥ 3** comorbidities; **30%** were **diabetics**

COVID-19, coronavirus disease 2019; SD, standard deviation
Available from: www.Gimbe.it; www.salute.gov.it

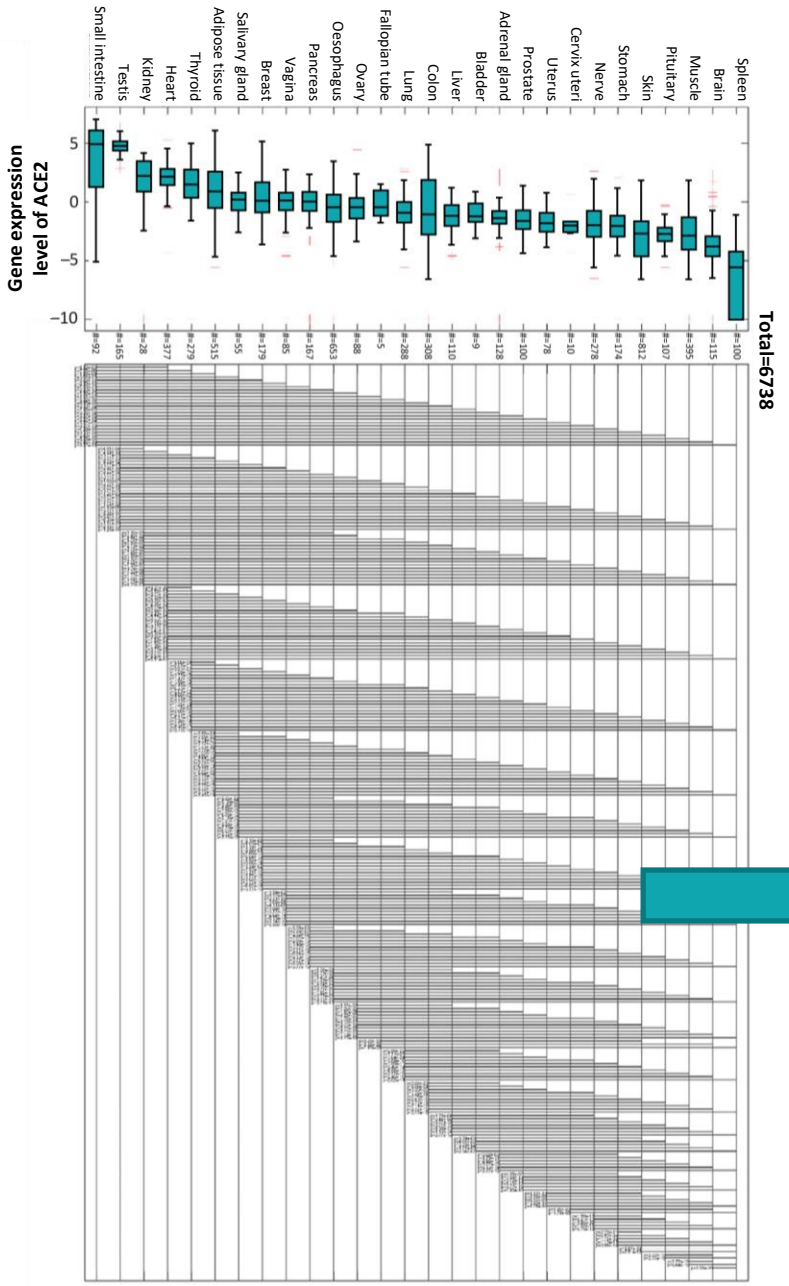
ENDOCRINE GLANDS/ORGANS THAT CAN BE AFFECTED BY COVID-19

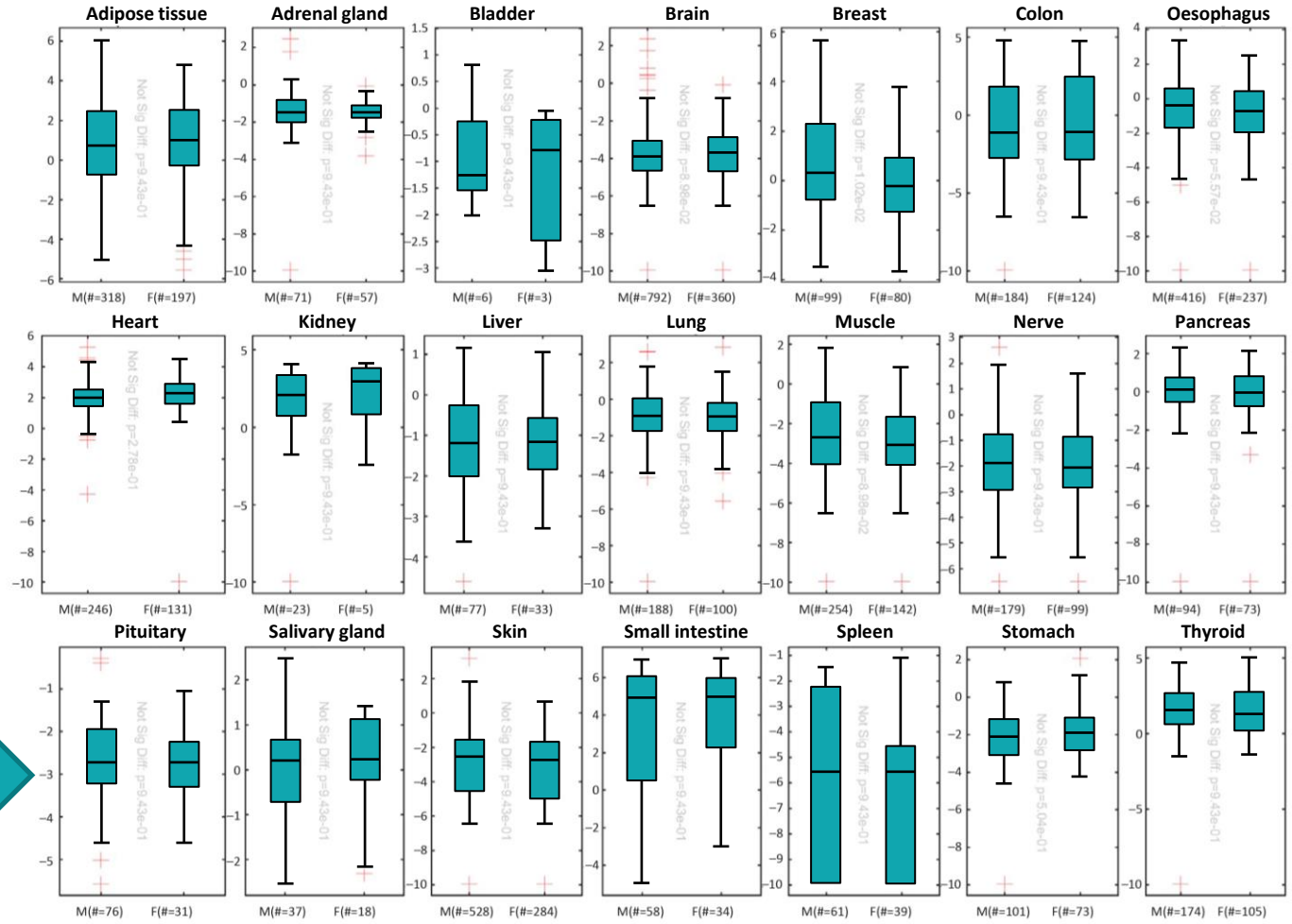


ATD, antithyroid drug; COVID-19, coronavirus disease 2019; SIADH, syndrome of inappropriate antidiuretic hormone secretion

Marazuela M et al.,. Rev Endocr Metab Disord. 2020;21:495-507.

ACE2 EXPRESSION IN ENDOCRINE TISSUES



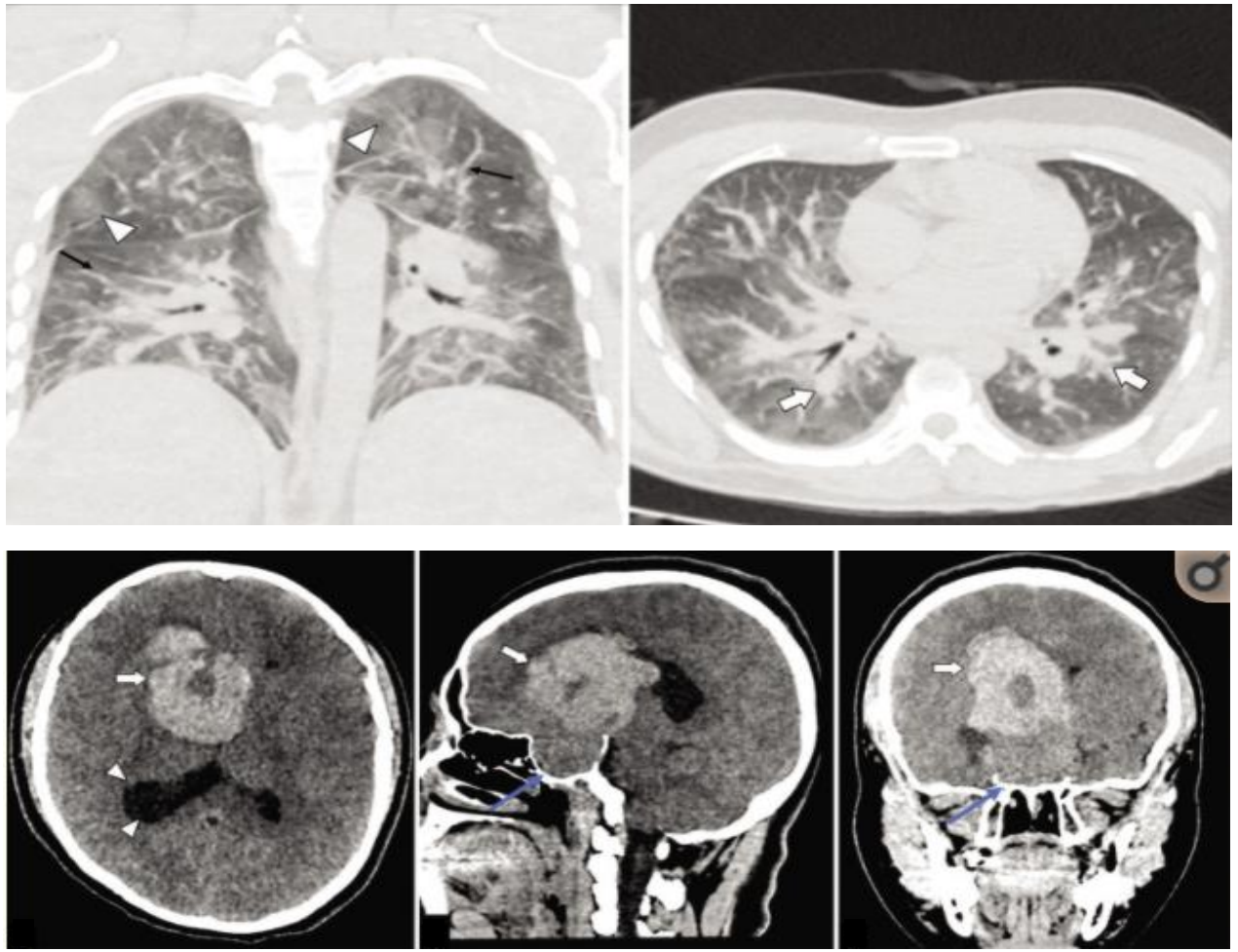


No significant differences

ACE2, angiotensin-converting enzyme 2; F, female; M, Male

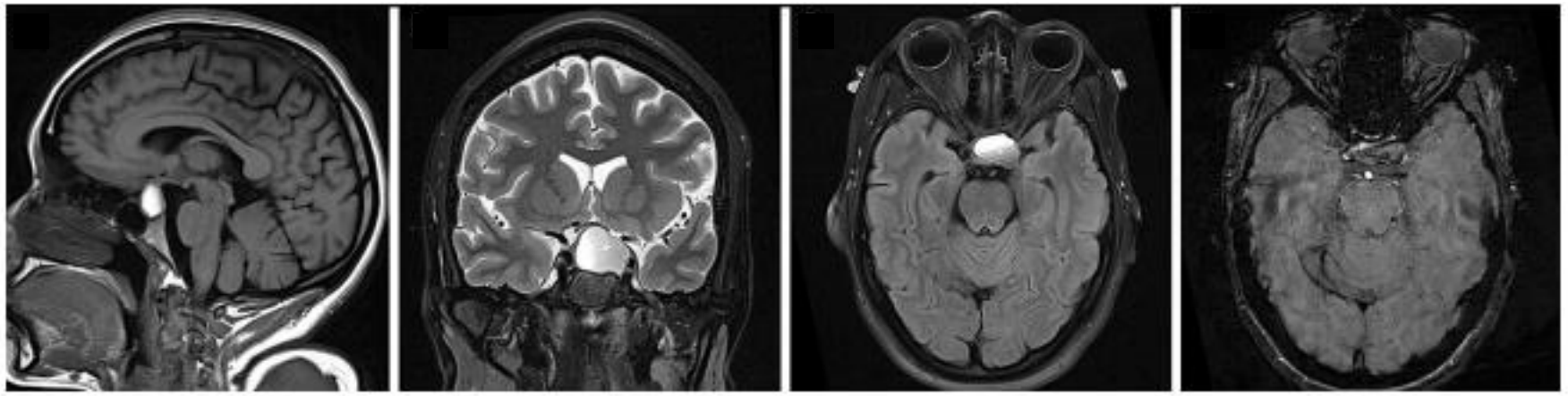
Han T, et al. Ann Transl Med. 2020;8:1077

PITUITARY APOPLEXY/1



Solorio-Pineda S, et al. Surg Neurol Int. 2020;11:304

PITUITARY APOPLEXY/2



Pre-operative (1 week after symptom onset) and post-operative (2 months) hormone levels

Hormone	Reference value (range)	Pre-op	Post-op
Prolactin, ng/mL	5.2–26.5	148.7	33.8
Cortisol (AM), µg/dL	3.7–19.4	3.9[a]	12.4
ACTH, pg/mL	6–50	< 5	16
TSH, mIU/L	0.39–4.60	0.28	< 0
T4 (free), ng/dL	0.70–1.48	0.47	1.16[b]
FSH, mIU/L	2.6–8.1	< 0.1	2.6
LH, mIU/L	24–105	4.6	3.7
IGF-1, ng/mL	63–373	103	143

[a] Taking dexamethasone 8 mg/day; [b] Taking levothyroxine 100 µg/day

ACTH, adrenocorticotrophic hormone; FSH, follicle-stimulating hormone; LH, luteinising hormone; TSH, thyroid-stimulating hormone; T4, thyroxine

Chan JL, et al. Pituitary. 2020;23:716–20

LITERATURE REVIEW OF 10 REPORTED CASES OF PA IN THE SETTING OF CONFIRMED COVID-19 INFECTION

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Investigator	Patient	Notable comorbidities	PA presentation	COVID-19 respiratory severity	MRI findings	Outcome
Bordes et al.	65 year-old female	Hypertension	Frontal headache phonophobia, photophobia	Not severe	1.4 cm Heterogeneous component without identifiable adenoma	Corticosteroid therapy and discharged
Solorio-Peneda et al.	27-year-old male	Unremarkable	Frontal headache, altered mental status, decreased visual acuity	Severe	5.9 × 5.2 × 6.8 cm Heterogeneous sellar mass	Died of pulmonary complications; surgical intervention of PA not initiated
Ghosh et al.	44-year-old female	Unremarkable	Severe headache, diplopia	Not severe	2.4 × 2.5 × 3.1 cm Heterogeneous cystic sellar Mass with fluid–fluid levels	Patient refused surgical intervention; discharge with slow symptom improvement at follow-up
Chan et al.	28-year-old female	Pregnant in third trimester	Mild headache, vision loss in left eye	Not severe	2.2 × 2.5 × 2.0 cm Cystic and haemorrhagic sellar mass with enlarged sella	TSS after delivery; discharge with complete recovery
dos Santos a Santos et al.	47-year-old male	Unremarkable	Frontal headache, diplopia, vision loss in left eye	Not severe	1.9 × 2.8 × 2.0 cm Hyperdense sellar mass with optic chiasm impingement	TSS; discharge with complete recovery
Katti et al.	46-year-old male	Unremarkable	Headache, acute bilateral vision loss	Not severe	3.4 × 3.0 × 2.4 cm Heterogeneous sellar/ suprasellar mass with optic chiasm impingement	Corticosteroid therapy and discharge
LaRoy et al.	35-year-old male	Unremarkable	Severe retro-orbital headache, neck stiffness	Not severe	0.7 × 0.8 × 0.8 cm Small hyperdense blood collection within sella turcica	Discharge
Present study	54-year-old female	Unremarkable	Holocranial headache, blurry vision	Not severe	2.8 cm Hyperdense sellar mass	Transcranial resection; discharge
Present study	56-year-old male	Obesity, hypertension, hypothyroidism	Headache, diplopia	Not severe	1.8 cm Sellar mass with interval enlargement and acute haemorrhage	TSS; discharge
Present study	52-year-old male	Obesity, hypertension	Peripheral vision loss, impotence	Not severe	Sellar lesion with suprasellar extension and T1-weighted hyperintense fluid level	TSS; discharge

COVID-19, coronavirus disease 2019; MRI, magnetic resonance imaging; PA, pituitary apoplexy; TSS, transsphenoidal surgery

Martinez-Perez R, et al. World Neurosurg. 2021;152:e678–87

PITUITARY APOPLEXY/3

Summary of some of the reported precipitating factors for the development of pituitary tumour apoplexy	
Conditions	Head trauma Hypotension
Medications	Anticoagulants Dopamine agonist
Procedures	Surgery (cardiac surgery) Pituitary dynamic testing TRH, GnRH, CRH, insulin-induced hypoglycaemia
Others	History of irradiation History of hypertension

COVID-19?

COVID-19, coronavirus disease 2019; CRH, corticotropin-releasing hormone; GnRH, gonadotropin-releasing hormone; TRH, thyrotropin-releasing hormone
Solorio-Pineda S, et al. Surg Neurol Int. 2020;11:304

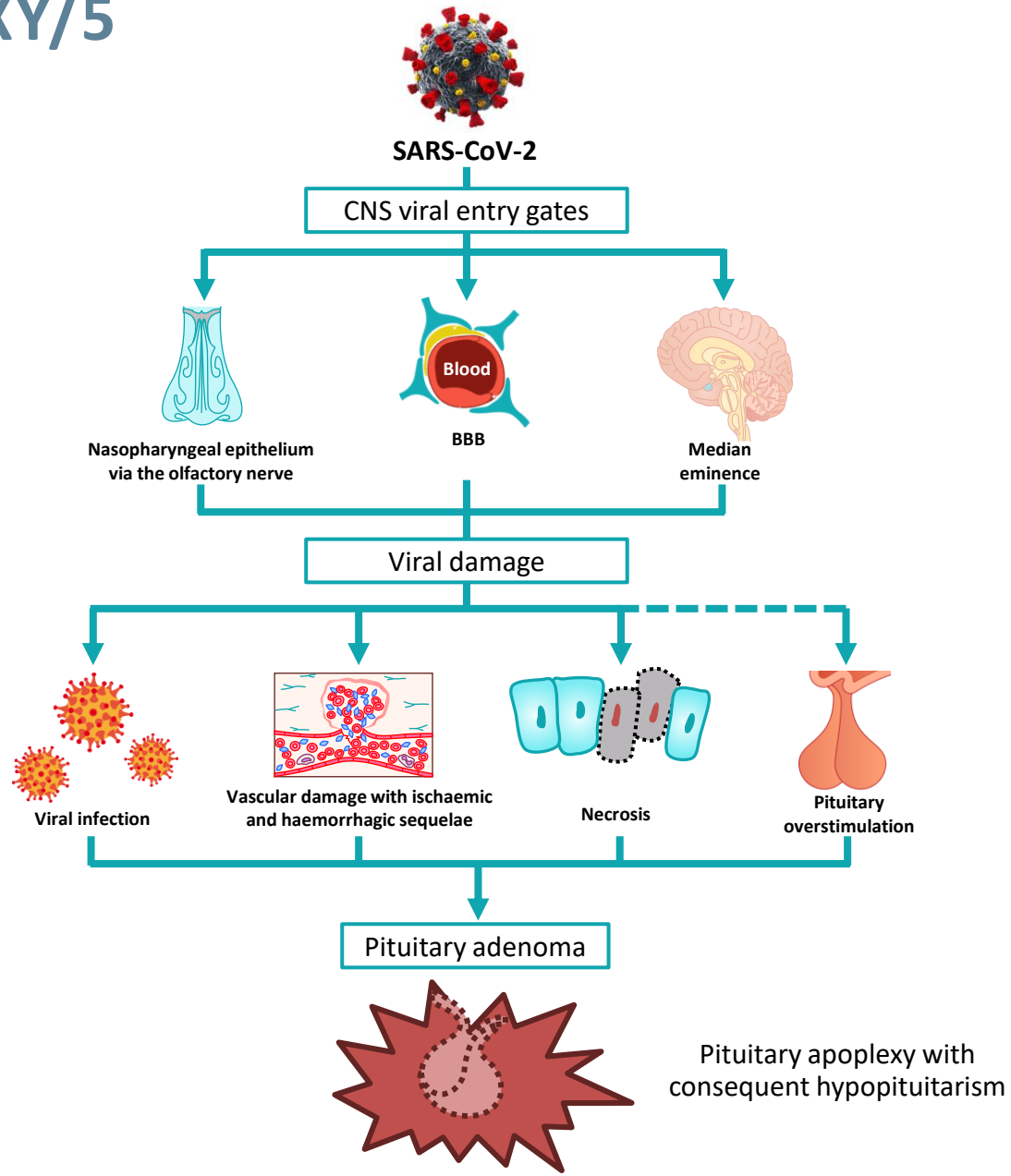
PITUITARY APOPLEXY/4

- COVID-19, particularly in the elderly, may be associated with a neurological phenotype including acute cerebrovascular disease with ischaemic stroke, cerebral venous thrombosis, or haemorrhage
- There is evidence of the presence of the SARS-CoV-2 virus in cerebrospinal fluid which increases the likelihood of viral relationship with bleeding processes
- Some authors report on the possibility of the virus entering the brain through the nasopharyngeal epithelium via the olfactory nerve, or passing through the BBB or directly reaching the median eminence, a circumventricular organ lacking the BBB

BBB, blood–brain barrier; COVID-19, coronavirus disease 2019; SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus 2

Solorio-Pineda S, et al. Surg Neurol Int. 2020;11:304

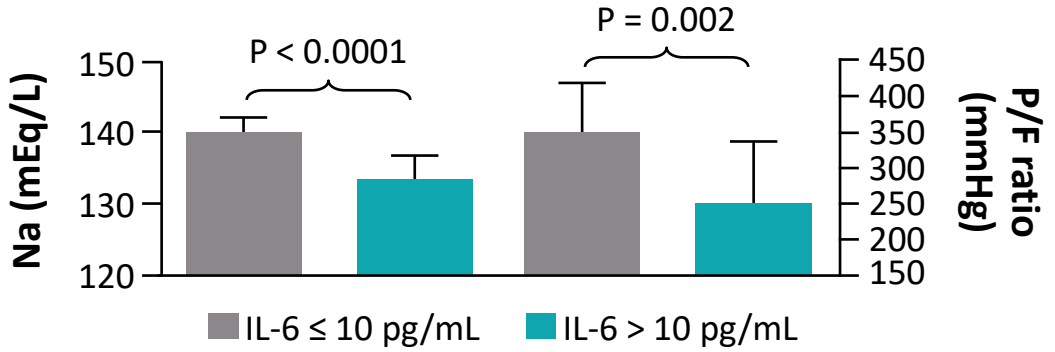
PITUITARY APOPLEXY/5

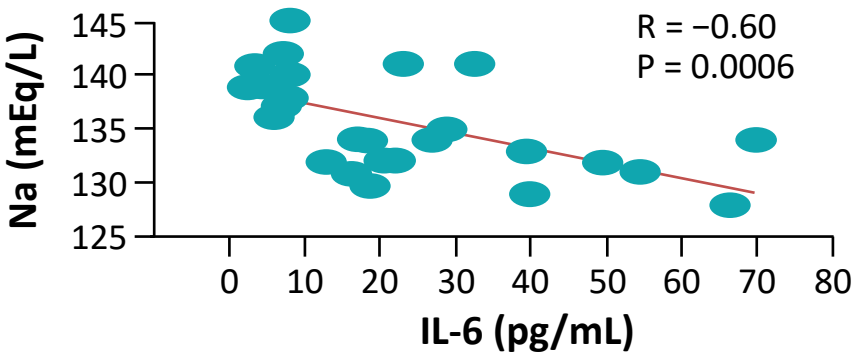


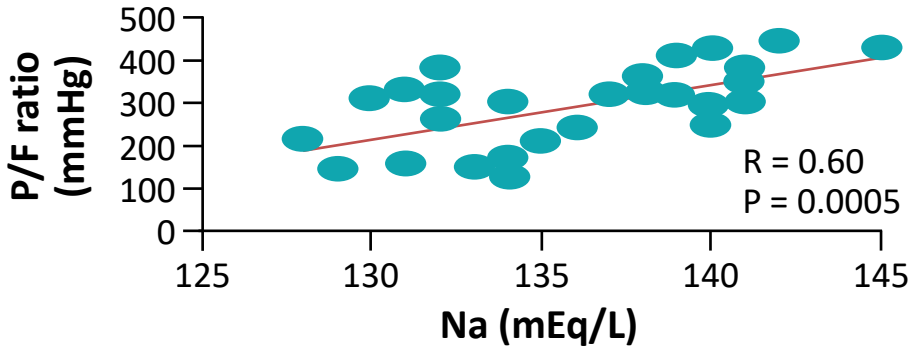
BBB, blood–brain barrier; CNS, central nervous system; SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus 2

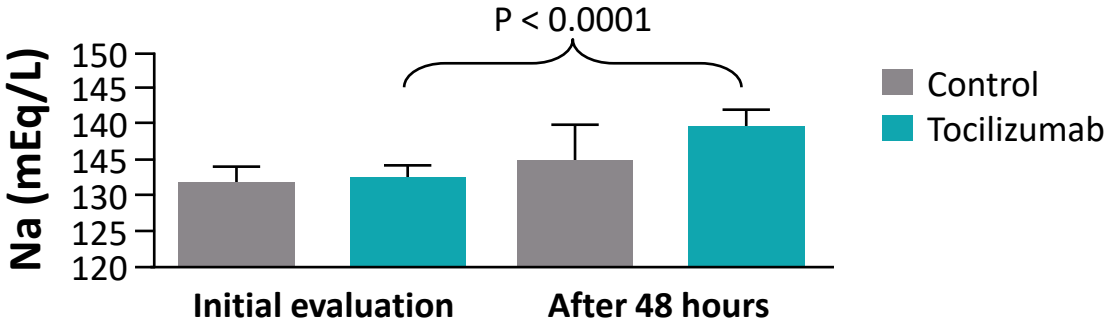
Frara S, et al. Rev Endocr Metab Disord. 2021. https://doi.org/10.1007/s11154-021-09672-y

SIADH/HYPONATRAEMIA/1









IL-6, interleukin 6; P/F, PaO_2/FiO_2; SIADH, syndrome of inappropriate antidiuretic hormone secretion

Berni A, et al. J Endrocrinol Invest. 2020;43:1137–9

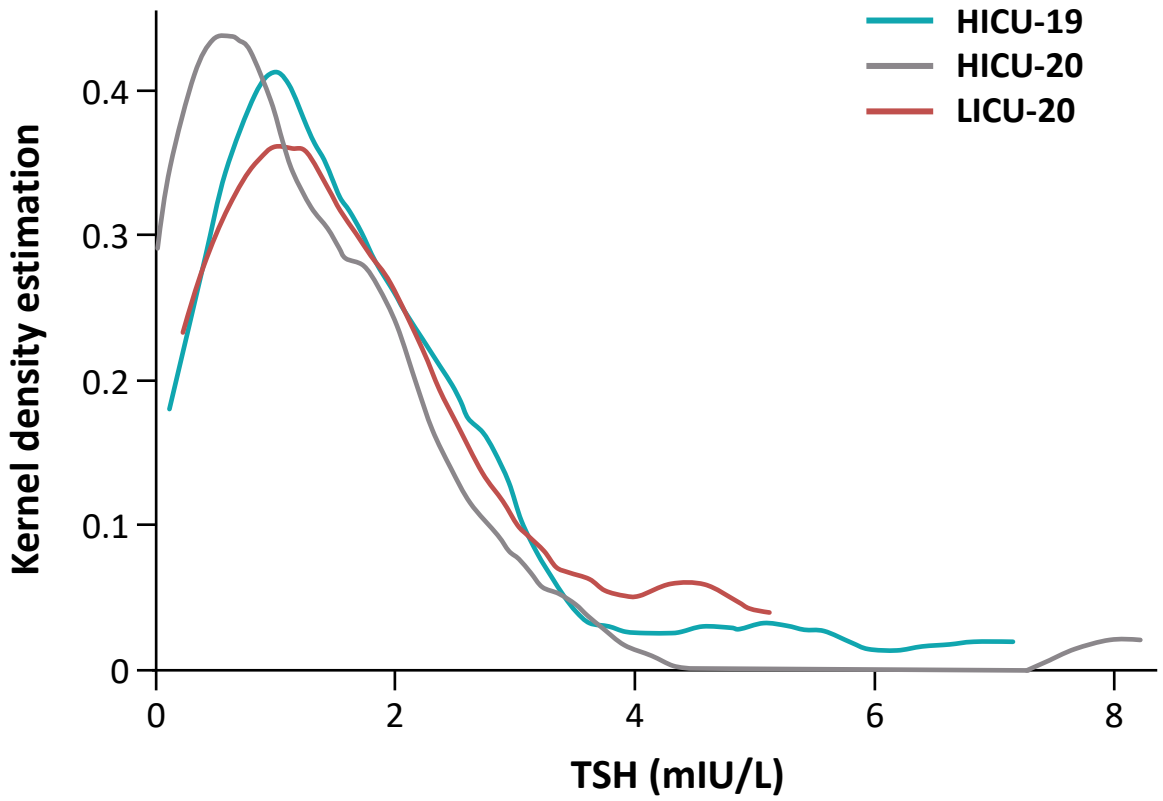
SIADH/HYPONATRAEMIA/2

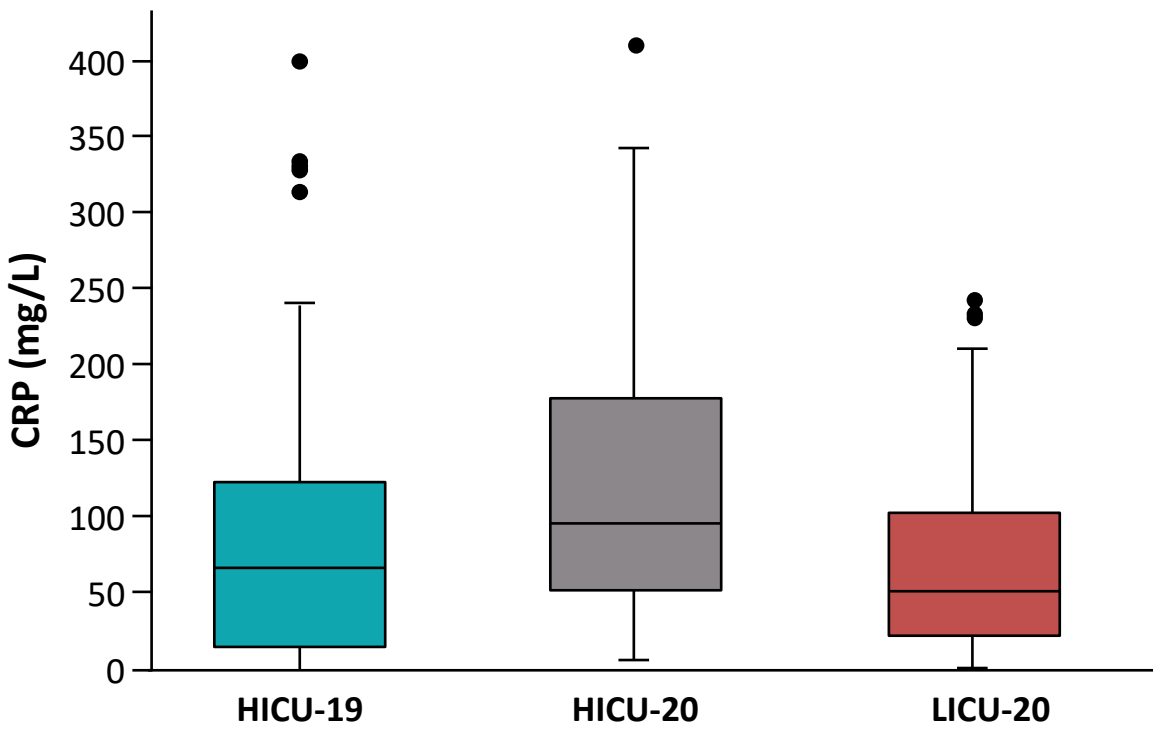
- Infectious diseases and several inflammatory conditions may be complicated by SIADH. In these situations, IL-6, released by monocytes and macrophages, may cause electrolyte impairment by inducing the non-osmotic release of vasopressin
- Na^+ might represent a biomarker of COVID-19 severity since low Na^+ appears to be inversely related to IL-6 and directly related to the P/F ratio, an important index of respiratory performance
- The significant increase of Na^+ 48 hours after the initiation of tocilizumab treatment further suggests the presence of an association between IL-6, vasopressin release, and ultimately Na^+ itself

COVID-19, coronavirus disease 2019; IL-6, interleukin 6; P/F, PaO_2/FiO_2; SIADH, syndrome of inappropriate antidiuretic hormone secretion

Berni A, et al. J Endrocrinol Invest. 2020;43:1137–9

HYPOPHYSITIS?/1





CRP, C-reactive protein; HICU-19, high intensity of care units (2019); HICU-20, high intensity of care units (2020); LICU-19, low intensity of care units (2019); TSH, thyroid-stimulating hormone

Muller I, et al. Lancet Diabetes Endocrinol. 2020;8:739–41

HYPOPHYSITIS?/2

- Treatment with ICIs is effective against several cancer types. The use of anti-PD-1, anti-PD-L1, and anti-CTLA-4 antibodies is expanding rapidly. The side effects include hypophysitis[1]
- The impact of ICIs on the clinical outcome of infections in humans is not well studied. Enhanced clearance of many pathogens has been shown because ICI activates T cells. In contrast, reactivation of tuberculosis associated with ICI use has been reported, and therefore caution is warranted in COVID-19 pneumonia[1]
- Recently a case of CDI due to infundibulo-neurohypophysitis as a late complication of COVID-19 was reported[2]

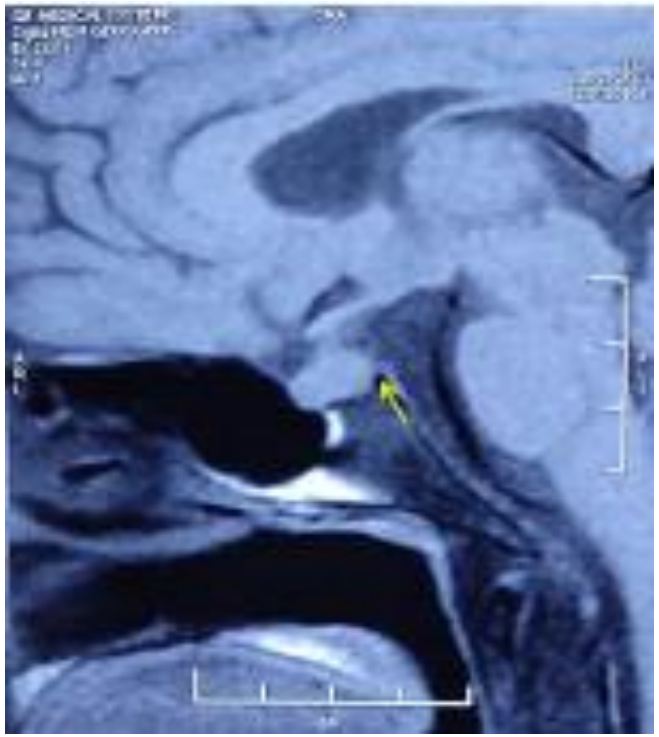
CDI, central diabetes insipidus; COVID-19, coronavirus disease 2019; CTLA-4, cytotoxic T lymphocyte-associated antigen-4; ICI, immune-checkpoint inhibitor/inhibition; PD-1, programmed death-1; PD-L1, programmed cell death ligand-1

1. Hamashima R, et al. Cancer Treat Rev. 2020;90:102109; 2. Misgar RA, et al. J Endrocrinol Invest. 2021. doi: 10.1007/s40618-021-01627-z

HYPOPHYSITIS IN COVID-19

(A) T1-weighted MRI showing enlarged pituitary with absent posterior pituitary bright spot (yellow arrow);
(B) Post contrast MRI showing thickened and enhanced pituitary stalk (red arrow)

(A)



(B)

COVID-19, coronavirus disease 2019; MRI, magnetic resonance imaging
Misgar RA, et al. J Endrocrinol Invest. 2021. doi: 10.1007/s40618-021-01627-z

COVID-19 AND PITUITARY ADENOMAS

- Acromegaly
- Cushing disease
- Pituitary surgery

COVID-19 AND ACROMEGALY

- Projected global costs of the COVID-19 pandemic are between $8.1 and $15.8 trillion[1]
- Routine care of chronic conditions such as acromegaly may be affected disproportionately by reallocation of healthcare resources
- Patients may face the prospect of prolonged delays in both diagnosis and treatment in many centres worldwide under COVID-19 pandemic conditions

COVID-19, coronavirus disease 2019

1. Schwab J. 2020. Available from: www.weforum.org/agenda/2020/08/pandemic-fight-costs-500x-more-than-preventing-one-futurity?fbclid=IwAR0MdKIwh1_xrq7a28n-0oiDu23lXY52_-ksMSbKQxB0DQJfMXim4Gi2H9E

COVID-19 AND ACROMEGALY

THE ACROCOVID INTERNATIONAL PROJECT/1

- The objectives of this international survey were to:
  1. Document changes to acromegaly disease-management approaches as perceived by endocrinologists
  2. Better understand the management of patients living with acromegaly under COVID-19 conditions
  3. Identify potential new ways to manage patients in the changing clinical environment

COVID-19, coronavirus disease 2019
Giustina A, et al. Endocrine. 2021;71:273–80

COVID-19 AND ACROMEGALY

THE ACROCOVID INTERNATIONAL PROJECT/2

- Four surveys were conducted: **patient, endocrinologist,** neurosurgeon, and specialist nurses
- **Endocrinologist** survey results are presented here:
  - Only a small number of responses were received for the neurosurgeon and specialist nurse surveys; as such these were not reported
- Data cut-off was 27 July 2020
- Questionnaires for the surveys were drafted by a Steering Committee of acromegaly experts and conducted online using Google forms
- Respondent awareness was generated through social media campaigns conducted using the usual channels (Facebook, Twitter)

COVID-19, coronavirus disease 2019
Giustina A, et al. Endocrine. 2021;71:273–80

COVID-19 AND ACROMEGALY

THE ACROCOVID INTERNATIONAL PROJECT/3

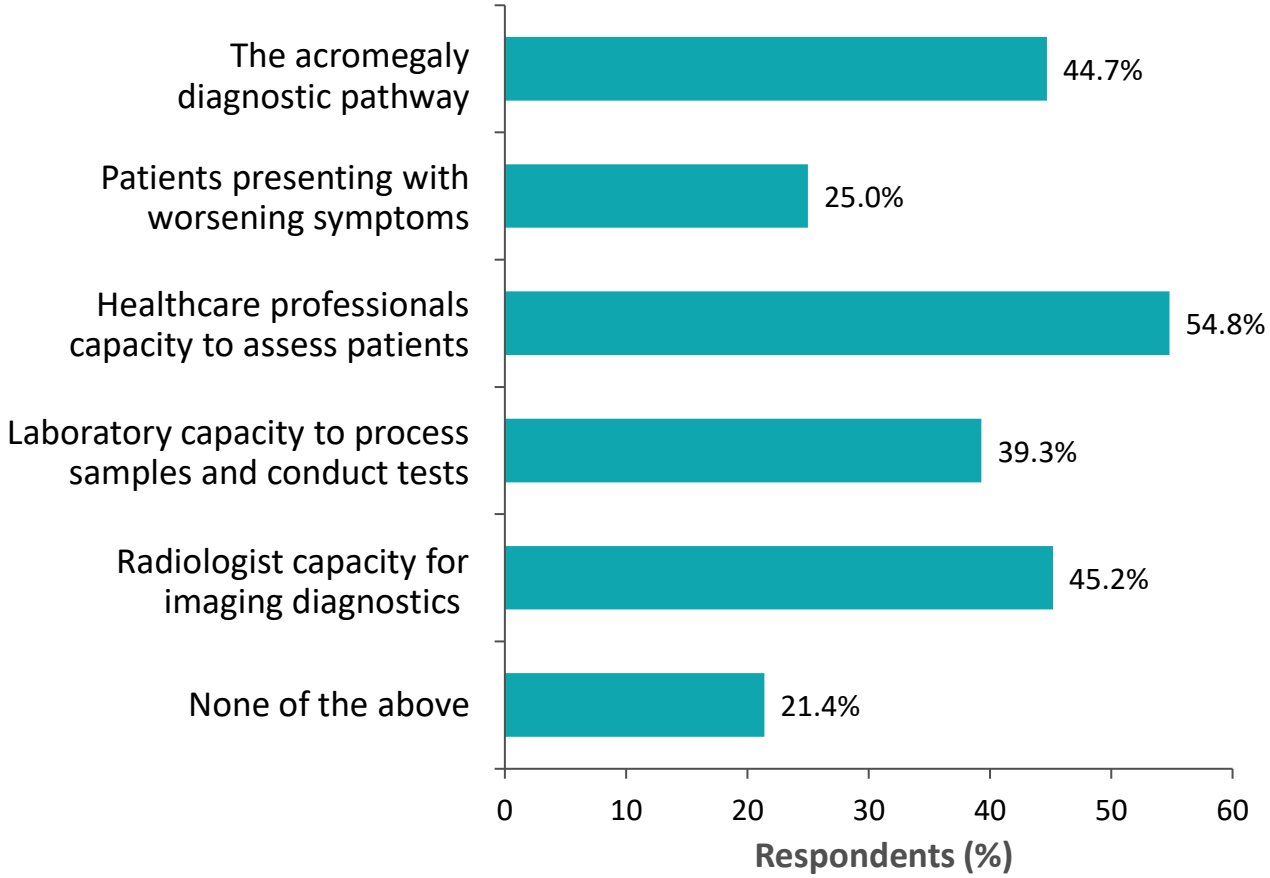
	Endocrinologist respondents, n (%) (N = 84)
Region	
Europe	57 (67.9)
North America	7 (8.3)
South America	16 (19.1)
Asia	4 (4.8)
Australia/Oceania	0
Africa	0
Female	49 (58.3)
Male	35 (41.7)
Practice type	
General endocrinology	40 (47.6)
Pituitary centre	44 (52.4)
Number of patients with acromegaly under ongoing care	
1–20	27 (32.1)
21–50	17 (20.2)
51–100	20 (23.8)
> 100	20 (23.8)

- The majority of respondents were based in Europe (67.9%) and identified as female (58.3%)
- Slightly more than half of respondents (52.4%) worked in a specialised pituitary centre
- The majority (47.6%) cared for > 50 patients with acromegaly

COVID-19, coronavirus disease 2019
Giustina A, et al. Endocrine. 2021;71:273–80

ASPECTS OF PATIENT MANAGEMENT MOST AFFECTED BY THE COVID-19 PANDEMIC

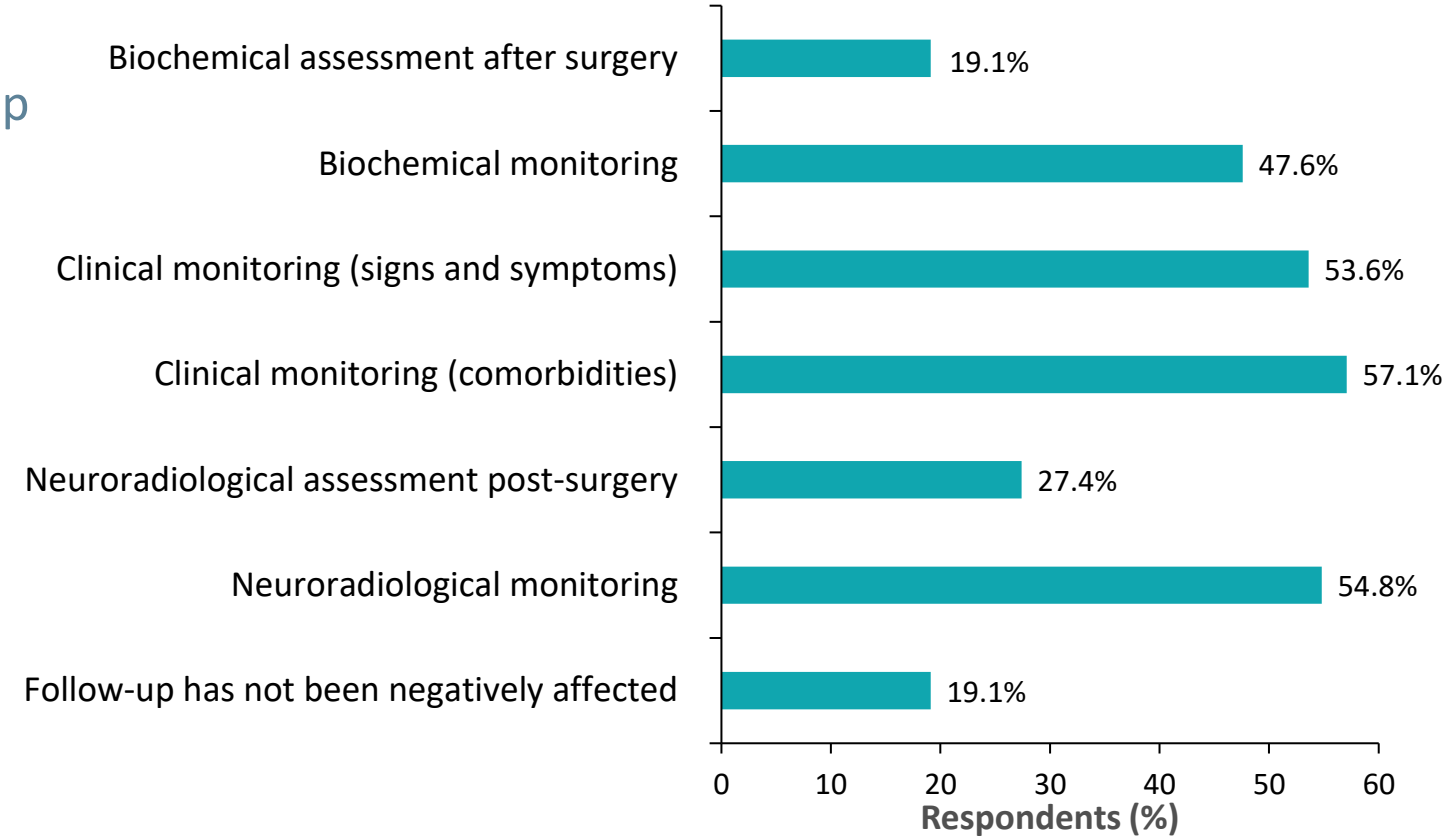
- Only 21.4% of respondents reported no negative effect on diagnostic practice



Data indicate percentage of respondents reporting a negative effect in each specific area of patient management (N = 84)
COVID-19, coronavirus disease 2019
Giustina A, et al. Endocrine. 2021;71:273–80

ASPECTS OF PATIENT FOLLOW-UP MOST AFFECTED BY THE COVID-19 PANDEMIC

- Only 19.1% of respondents reported no negative effect on patient follow-up



COVID-19, coronavirus disease 2019
Giustina A, et al. Endocrine. 2021;72:596

ASPECTS OF PATIENT FOLLOW-UP/MANAGEMENT MOST AFFECTED BY THE COVID-19 PANDEMIC/1

- SRLs are able to control tumour growth and induce tumour shrinkage in most patients with acromegaly,[1,2] and can be a valid option when when surgery is delayed.[3] This consideration is increasingly important currently given that many endocrinologists have reported major difficulties in the neuroradiological follow-up of their patients

- Another challenge that emerged from the survey was the difficultly in monitoring biochemical control of acromegaly, which at present still represents the milestone for evaluating the efficacy of treatment[4,5]

COVID-19, coronavirus disease 2019; SRL, somatostatin receptor ligand

1. Giustina A, et al. PLoSOne. 2012;7:e36411; 2. Mazziotti G, Giustina A. Pituitary. 2010;13:60–7; 3. Giustina A, et al. Rev Endocr Metab Disord. 2020;21:667–78; 4. Giustina A, et al. J Clin Endocrinol Metab. 2000;85:526–9; 5. Giustina A, et al. J Clin Endocrinol Metab. 2010;95:3141–8

ASPECTS OF PATIENT FOLLOW-UP/MANAGEMENT MOST AFFECTED BY THE COVID-19 PANDEMIC/2

- Poor monitoring can significantly affect adequate management of acromegaly by postponing SRL dose escalation[1,2] or switching to another SRL[3] or alternative treatment like pegvisomant[4]

- Importantly, while SSAs have only marginal effects on glucose metabolism,[5] even when used at high doses,[6] use of pasireotide may impair glucose homeostasis and, conversely, pegvisomant may improve it[7]

- The potential impact of these glucoactive effects should not be overlooked in the context of COVID-19 which, in addition to the poor prognosis related to existing impaired metabolism, can induce severe complications related to glucose metabolism such as ketoacidosis[8]

COVID-19, coronavirus disease 2019; SRL, somatostatin receptor ligand; SSA, somatostatin analogue

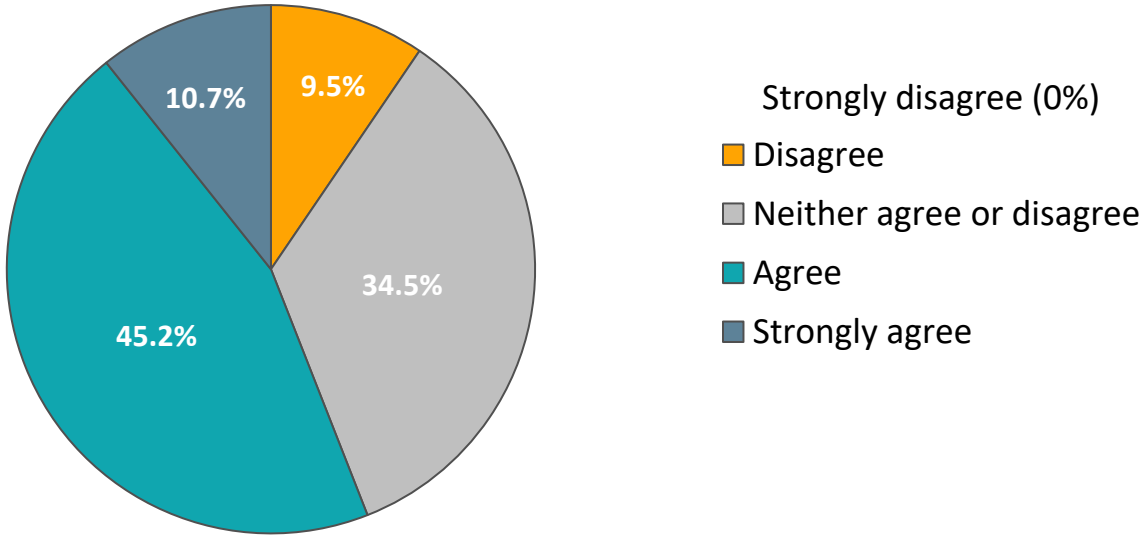
1. Giustina A, et al. Eur J Endocrinol. 2009;161:331–8; 2. Giustina A, et al. J Clin Endocrinol Metab. 2017;102:2454–64; 3. Gadelha MR, et al. Lancet Diabetes Endocrinol. 2014;2:875–84; 4. Giustina A, et al. J Endocrinol Invest. 2017;40:577–89; 5. Mazziotti G, et al. J Clin Endocrinol Metab. 2009;94:1500–8; 6. Mazziotti G, et al. Eur J Endocrinol. 2011;164:341–7; 7. Frara S, et al. Trends Endocrinol Metab. 2016;27:470–83; 8. Smith SM, et al. J Med Virol. 2021;93:409–15

ACROCOVID

PATIENT-PERCEIVED RISK AND COMMUNICATION WITH PATIENTS IN THE COVID-19 PANDEMIC

- 76.2% of endocrinologists were approached regarding being at an increased risk
  - 41.7% reported their patients had sought their advice regarding disease management and 59.5% regarding medical therapy
- Few endocrinologists approached their patients regarding general health (10.7%), acromegaly management (14.3%), and medical therapy (16.7%)
- 47.6% reported a negative effect on their relationships with patients
  - 53.6% reported reduced contact
  - 4.8% reported only allowing urgent visits
  - 1.2% reported suspending services entirely

- Many respondents experienced a degree of success with remote patient management



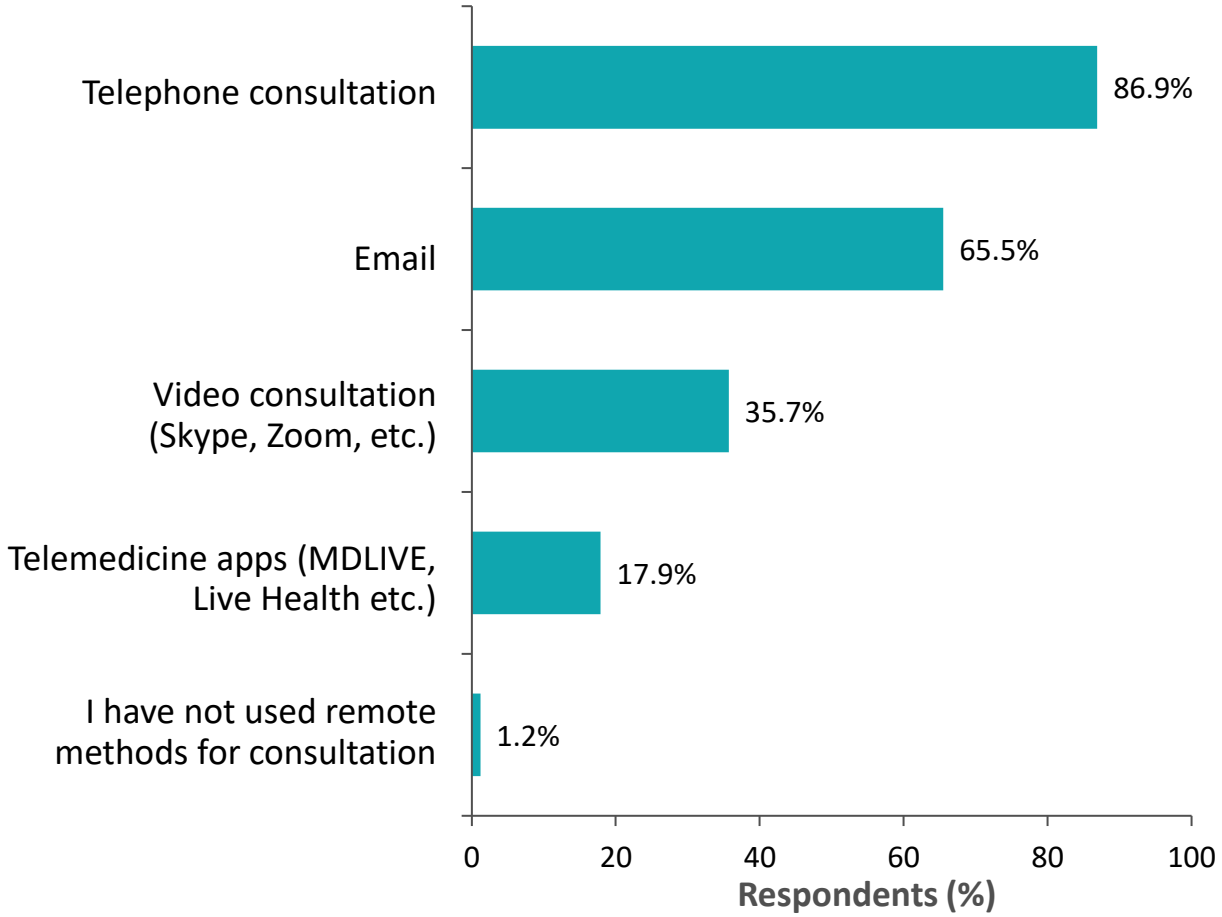
Percentage of endocrinologists agreeing with the below statement:

Remote consultation improved my ability to communicate to patients with acromegaly during the COVID-19 pandemic

N = 84
COVID-19, coronavirus disease 2019
Giustina A, et al. Endocrine. 2021;71:273–80

HOW ARE ENDOCRINOLOGISTS COMMUNICATING WITH THEIR PATIENTS UNDER COVID-19 PANDEMIC CONDITIONS?

- Remote consultations were most commonly used to conduct post-diagnosis discussions (76.2%) and to discuss adverse events related to treatment (64.3%)
- 69.0% of respondents indicated that they would continue to use remote methods after the pandemic



Data indicate percentage of respondents reporting having used each communication method under COVID-19 pandemic conditions
Note that each respondent is able to indicate more than one method (N = 84)
COVID-19, coronavirus disease 2019
Giustina A, et al. Endocrine. 2021;71:273–80

SRLs UNDER COVID-19 PANDEMIC CONDITIONS: IN-HOSPITAL VS SELF/PARTNER-ADMINISTERED/1

- 50% of respondents indicated that they believed that the role of self/partner-administered injections was of increased importance under pandemic conditions
  - 33.5% recommended a switch to self/partner-administered SRLs in patients lacking biochemical control
  - Only 9.5% recommended delaying monthly SRLs treatment to avoid possible patient exposure to COVID-19

N = 84
COVID-19, coronavirus disease 2019; SRL, somatostatin receptor ligand
Giustina A, et al. Endocrine. 2021;71:273–80

SRLs UNDER COVID-19 PANDEMIC CONDITIONS: IN-HOSPITAL VS SELF/PARTNER-ADMINISTERED/2

- Use of self-administered SSAs without the need of house visits from healthcare professionals or even hospital visits for injection were demonstrated to be of increased importance during the pandemic and, likely, also for future clinical management[1,2]
- The possibility of orally administered SSAs[3,4] may have clinical implications for simplified management of well controlled disease in emergency situations such as the COVID-19 pandemic

N = 84; COVID-19, coronavirus disease 2019; SSA, somatostatin analogue

1. Salvatori R, et al. Pituitary. 2010;13:115–22; 2. Salvatori R, et al. Pituitary. 2014;17:13–21;
3. Melmed S, et al. J Clin Endocrinol Metab. 2015;100:1699–708; 4. Samson SL, et al. J Clin Endocrinol Metab. 2020;105:e3785–97

THE ‘NEW’ NORMAL FOR ENDOCRINOLOGISTS/1

- COVID-19 is changing the clinical approach to acromegaly
- Endocrinologist respondents reported broad negative effects on the care pathway
  - More than half reported difficulties in the clinical monitoring of signs and symptoms
  - Biochemical control is necessary to evaluating efficacy of treatment[1,2]
  - Poor monitoring can affect adequate management significantly[3,4]
- Delays to surgical and radiotherapeutic treatments and the availability of inpatient services are concerning
  - However, it is important to note that care was continued in the vast majority of cases

COVID-19, coronavirus disease 2019

1. Giustina A, et al. J Clin Endocrinol Metab. 2000;85:526–9; 2. Giustina A, et al. J Clin Endocrinol Metab. 2010;95:3141–8;
3. Giustina A, et al. Eur J Endocrinol. 2009;161:331–8; 4. Giustina A, et al. J Clin Endocrinol Metab. 2017;102:2454–64

THE ‘NEW’ NORMAL FOR ENDOCRINOLOGISTS/2

- COVID-19 pandemic conditions provide an opportunity to create a new continuum of care
- Endocrinologists are interested in integrating innovative patient communication with novel methods of delivering therapies (e.g. SSAs)
  - Changes may improve patient care by reducing the burden of hospital visits
- Several issues will need to be resolved before these approaches can be routinely incorporated into endocrine practice:
  - Remote consultations are not recognised as equivalent for remuneration
  - There are legal concerns regarding data breaches if unsafe electronic media are employed

COVID-19, coronavirus disease 2019; SSA, somatostatin analogue
Giustina A, et al. Endocrine. 2021;71:273–80

COVID-19 AND CUSHING DISEASE

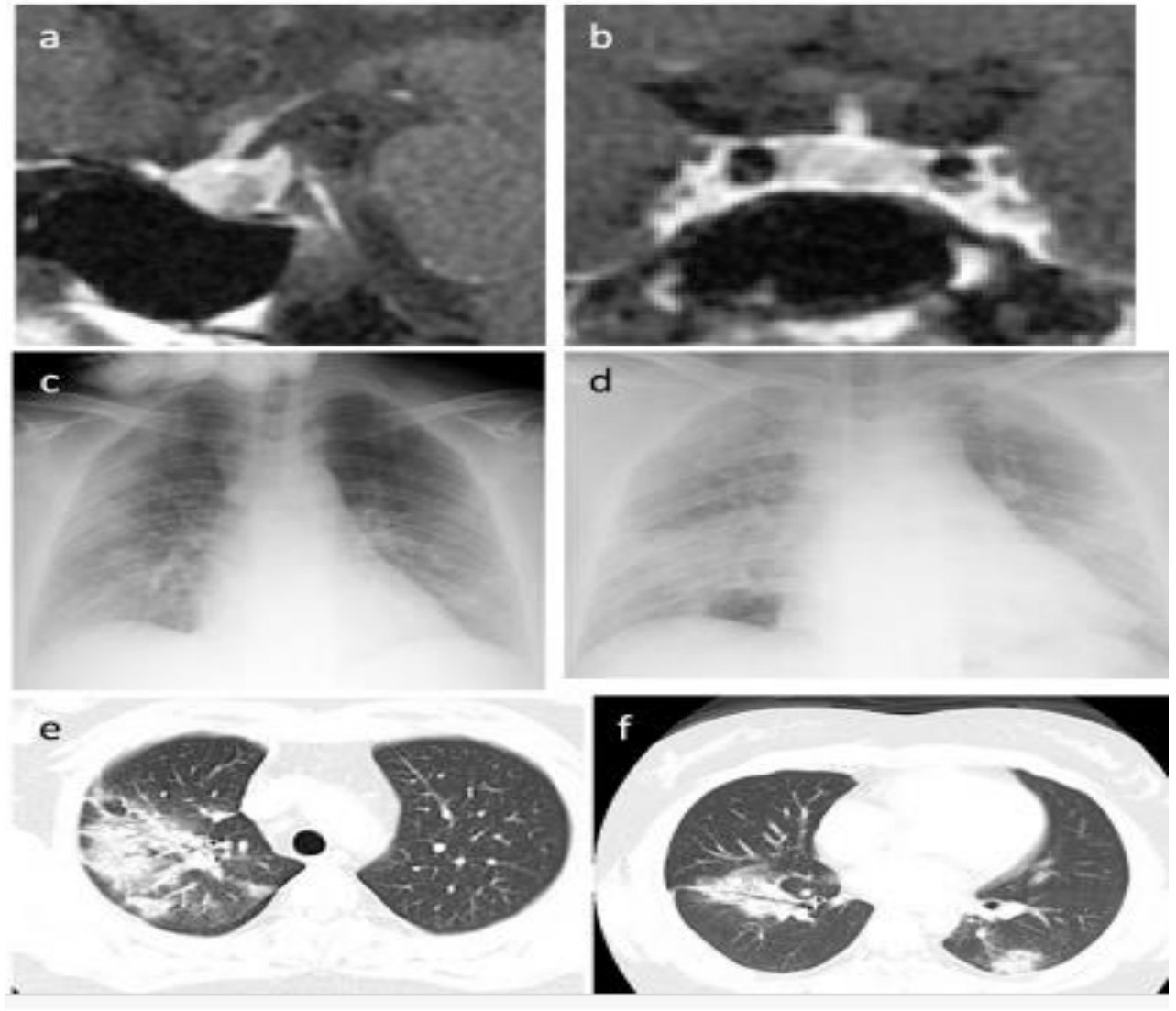
Characteristics of patients with Cushing disease and microincidentaloma in the context of the COVID-19 pandemic

	CD (N = 61)	Control (N = 61)
Age, years[a]	52.6 ± 12.4	52.7 ± 11.7
Female	51 (83.3)	51 (83.3)
Smoker	8 (13.1)	11 (18)
Influenza vaccination	20 (32.7)	16 (26.3)
Profession at risk	10 (16.4)	7 (11.5)
Daily travel for work	8 (13.1)	7 (11.5)
Use of public transportation	2 (3.2)	2 (3.2)
Cohabitants[b]	1 (0–5)	2 (0–5)
Signs and symptoms (≥ 1) of COVID-19: Jan to 15 Apr	23 (37.7)	29 (47.5)
Signs and symptoms (≥ 1) of COVID-19: Mar to 15 Apr	9 (14.7)	15 (24.6)
Signs and symptoms (≥ 1) of COVID-19: Mar to 15 Apr[b]	3 (1–7)	2 (1–6)
Cough and fever	4 (6.5)	1 (1.6)
Signs and symptoms (≥ 3) lasting ≥ 1 week: Mar to 15 Apr	4 (6.5)	2 (3.2)
Nasopharyngeal swab	2 (3.2)	3 (4.9)
COVID-19 positive	2 (3.2)	0

- 3.2% of patients with CD had confirmed COVID-19 compared with 0.6% of the general population in Lombardy by mid-April
- Severe clinical presentation was observed especially in patients with active CD, suggesting that chronic hypercortisolism may be associated with more serious SARS-CoV-2 infection
- Overall, our data indicate that patients with active CD should be considered a fragile population

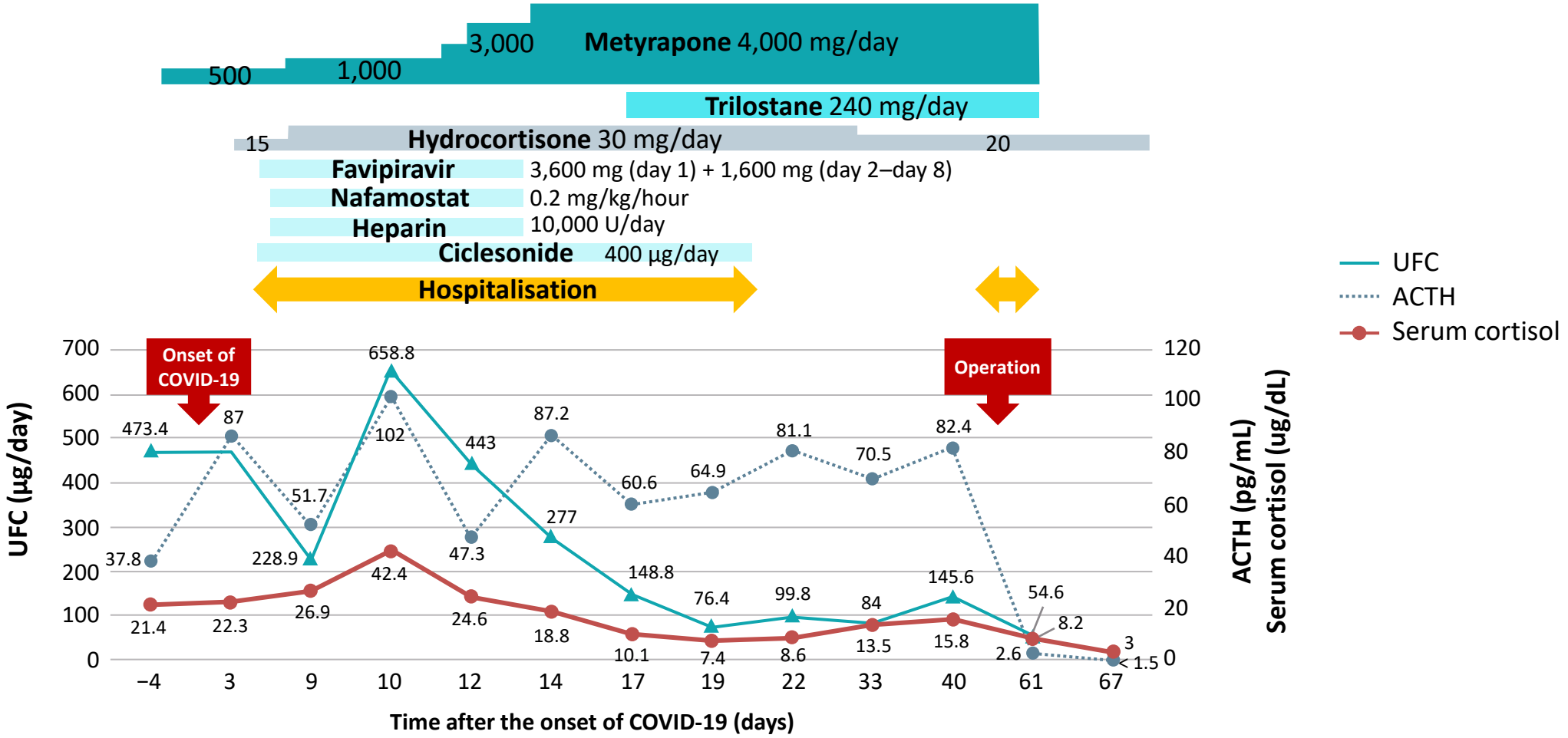
Data are expressed as n (%) unless stated otherwise; [a] Mean ± SD; [b] Median (range)
CD, Cushing disease; COVID-19, coronavirus disease 2019; SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus 2; SD, standard deviation
Serban AL, et al. J Endocrinol Invest. 2021;44:1335–6

COVID-19 AND CUSHING DISEASE



COVID-19, coronavirus disease 2019
Yuno A, et al. Endocr J. 2021;68:477–84

COVID-19 AND CUSHING DISEASE



ACTH, adrenocorticotrophic hormone; COVID-19, coronavirus disease 2019; UFC, urinary free cortisol

Yuno A, et al. Endocr J. 2021;68:477–84

COVID-19 AND CUSHING DISEASE

RISK FACTORS AND CLINICAL SUGGESTIONS FOR PATIENTS WITH CUSHING DISEASE WHO HAVE COVID-19/1

Reduction of febrile response and enhancement of dyspnoea

- Rely on different symptoms and signs suggestive of COVID-19, such as cough, dysgeusia, anosmia, and diarrhoea

Prolonged duration of viral infections and susceptibility to superimposed bacterial and fungal infections

- Consider prolonged antiviral and broad-spectrum antibiotic treatment

COVID-19, coronavirus disease 2019

Pivonello R, et al. Lancet Diabetes Endocrinol. 2020;8:654–6

COVID-19 AND CUSHING DISEASE

RISK FACTORS AND CLINICAL SUGGESTIONS FOR PATIENTS WITH CUSHING DISEASE WHO HAVE COVID-19/2

Impairment of glucose metabolism (negative prognostic factor)

- Optimise glycaemic control and select cortisol-lowering drugs that improve glucose metabolism.

Hypertension (negative prognostic factor)

- Optimise blood pressure control and select cortisol-lowering drugs that improve blood pressure

Thrombosis diathesis (negative prognostic factor)

- Start antithrombotic prophylaxis, preferably with low-molecular-weight heparin treatment

COVID-19, coronavirus disease 2019

Pivonello R, et al. Lancet Diabetes Endocrinol. 2020;8:654–6

PITUITARY SURGERY IN THE COVID-19 ERA

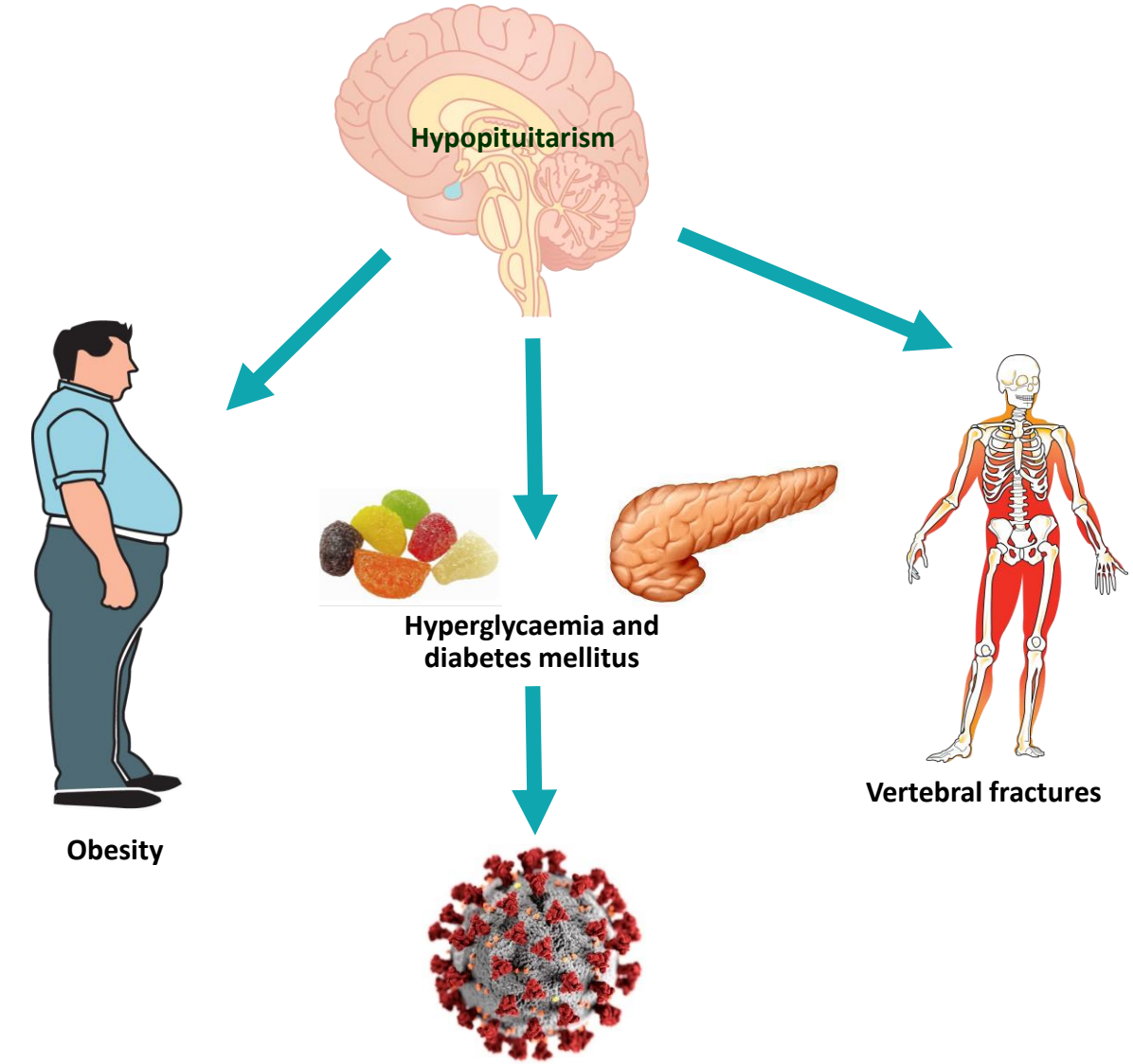
Factor	Challenges	Recommendations
COVID-19	High prevalence of cases in the community during pandemic and risk of additional waves in the post-peak phase	Screening for cough, fever, and other symptoms and, if suspected, swab for testing *Consider* • Isolation for up to 2 weeks before surgery • Paired swabs for testing and/or serological tests • Chest X-ray and/or chest CT
Patient	High risk of older patients with comorbid conditions contracting COVID-19; consider natural history of pituitary disease	Emergency surgery if pituitary apoplexy, acute severe visual loss, or other evidence of significant mass effect, or if there is concern regarding malignant pathology *Consider* Surgery for patients with less acute, but progressive visual loss, functioning tumours with aggressive clinical features, and those with an unclear diagnosis
Surgeon	Risk of surgeon contracting COVID-19 from patient	In a patient with COVID-19 that requires emergency surgery that cannot be deferred, alternative transcranial approaches may be considered, drilling avoided, and full PPE is mandated *Consider* • Full PPE in all cases
Institution	Diversion of resources to (non-pituitary) patients with COVID-19	Maintain flexibility for second wave

COVID-19, coronavirus disease 2019; CT, computerised tomography; PPE, personal protective equipment

Fleseriu M et al., Pituitary. 2020;23:327-337.

COVID-19 AND HYPOPITUITARISM

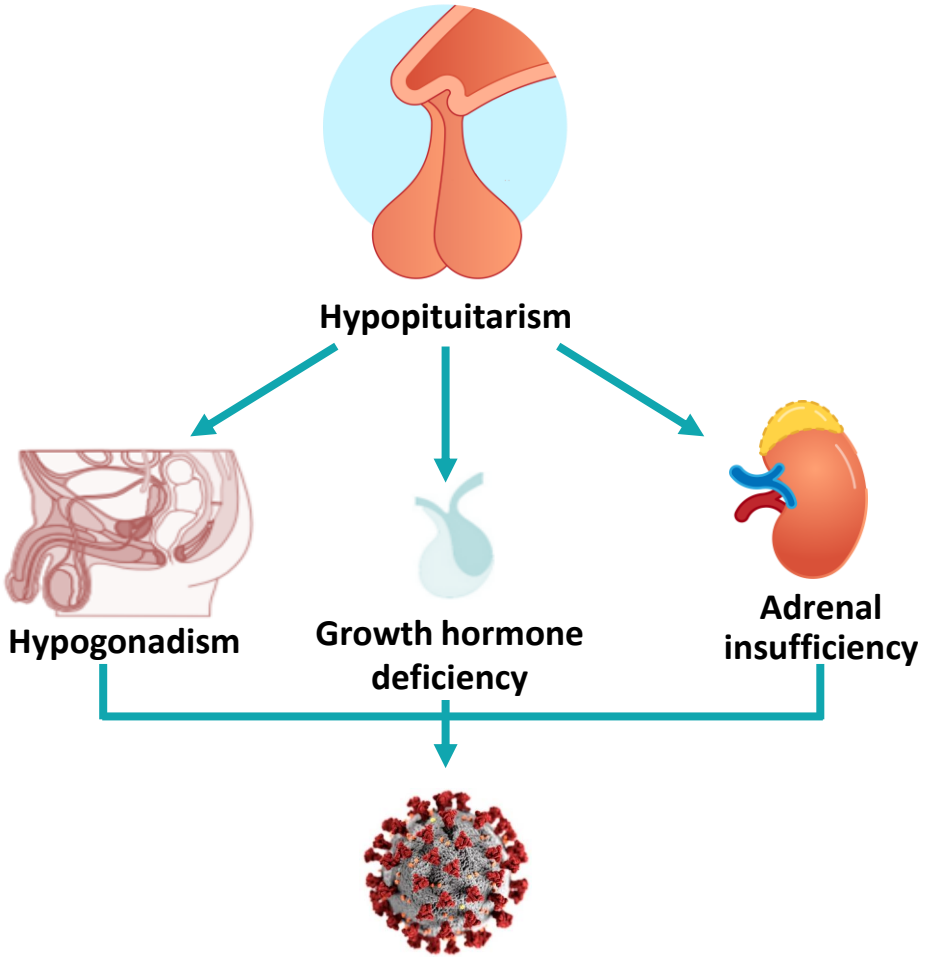
COMORBIDITIES OF HYPOPITUITARISM AND COVID-19



Frara S, et al. Rev Endocr Metab Disord. 2021. https://doi.org/10.1007/s11154-021-09672-y

CONTRIBUTION OF ENDOCRINE COMPONENTS OF HYPOPITUITARISM TO COVID-19 IMPACT

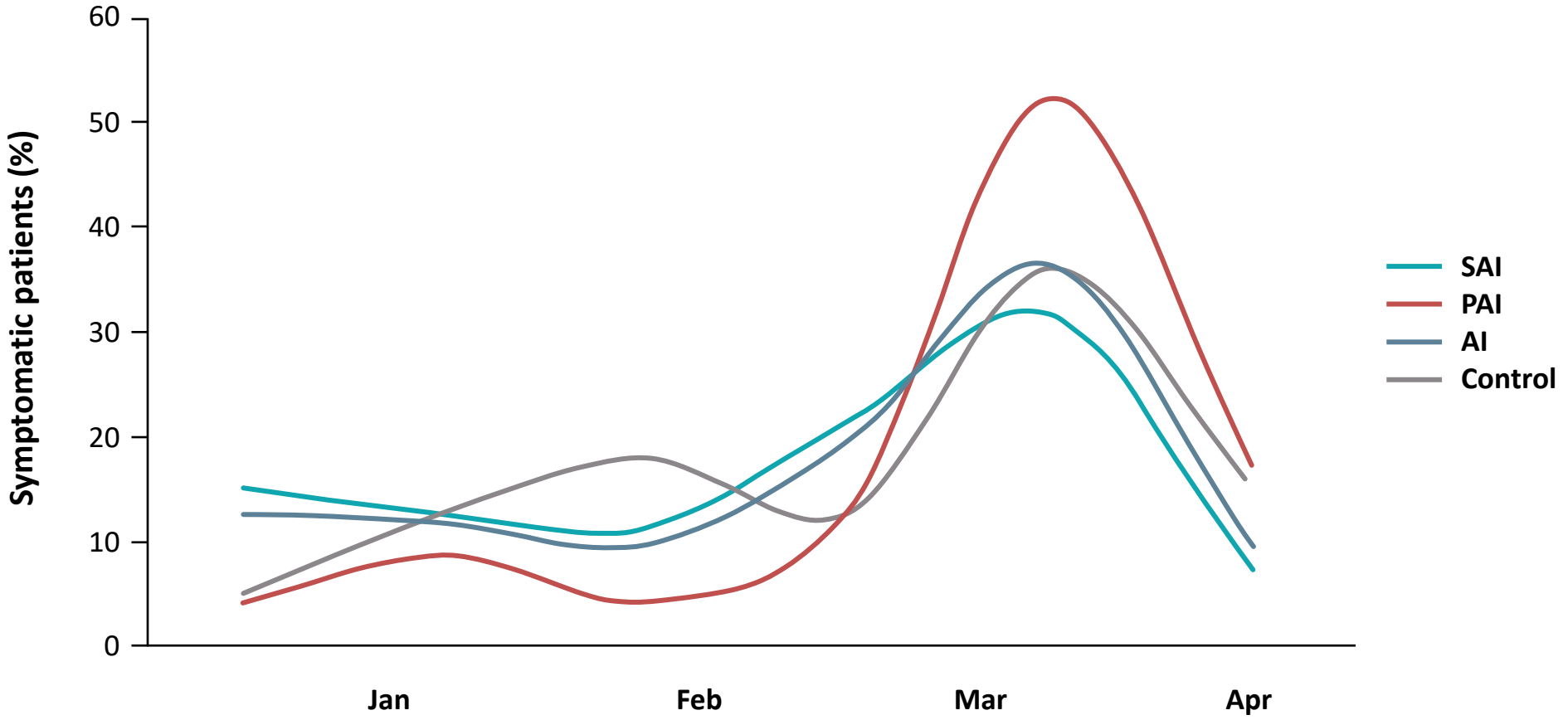
- Possible contribution of deficient pituitary-target gland axes to susceptibility to SARS-CoV-2 infection in hypopituitarism
- The figure illustrates the role of specific components of hypopituitarism, including hypogonadism, growth hormone deficiency, and adrenal insufficiency, possibly predisposing to SARS-CoV-2 infection and severe COVID-19



COVID-19, coronavirus disease 2019; SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus 2

Frara S, et al. Rev Endocr Metab Disord. 2021. https://doi.org/10.1007/s11154-021-09672-y

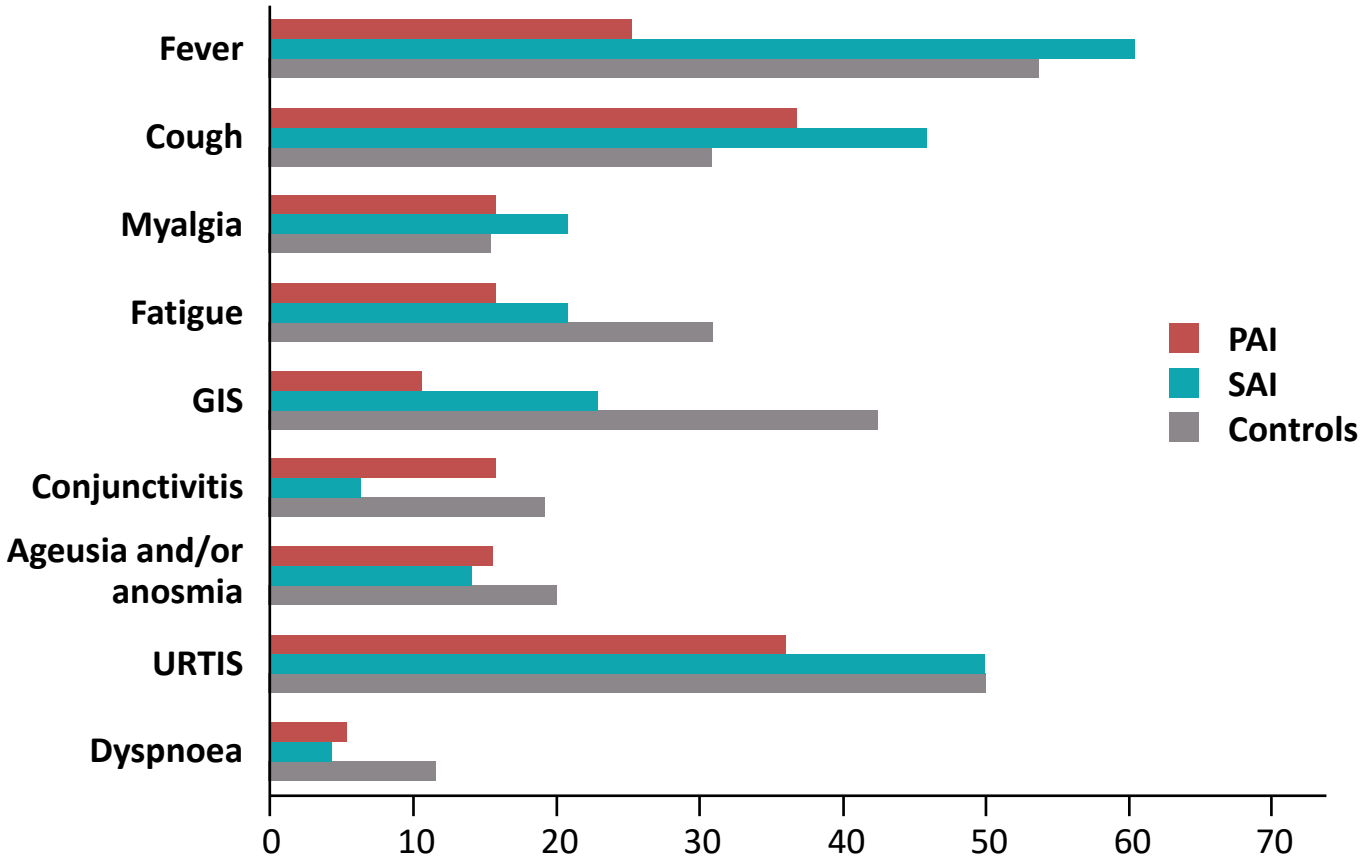
COVID-19 AND HYPOPITUITARISM/1



AI, adrenal insufficiency; COVID-19, coronavirus disease 2019; PAI, primary adrenal insufficiency; SAI, secondary adrenal insufficiency

Carosi G, et al. J Clin Endocrinol Metab. 2021;106:e1354–61

COVID-19 AND HYPOPITUITARISM/2



COVID-19, coronavirus disease 2019; GIS, gastrointestinal symptoms; PAI, primary adrenal insufficiency; SAI, secondary adrenal insufficiency; URTIS, upper respiratory tract infection symptoms

Carosi G, et al. J Clin Endocrinol Metab. 2021;106:e1354–61

COVID-19 AND HYPOPITUITARISM
SELECTED CASES – SAN RAFFAELE HOSPITAL

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CASE #1

- An 80-year-old patient with hypopituitarism and diabetes insipidus after surgery for craniopharyngioma in 1990, tested positive for SARS-CoV-2 at hospital admission for cardiogenic syncope
- He suffered from hypertension, mild diabetes, COPD, atrial fibrillation, vascular disease; he was on stable therapy with L-T4, high-dose cortisone acetate (62.5 mg/day), intranasal desmopressin, and anticoagulants
- He had no symptoms nor radiological signs specific for COVID-19. Blood tests showed hyponatraemia (Na^+ 128.3 mmol/L) and increased LDH (290 U/L), CRP (82 mg/L, RR < 6), IL-6 (262 pg/mL, RR < 7) and D-dimer (> 20 µg/mL, RR. 0.27–0.77)
- He received a supplemental dose of parenteral hydrocortisone, optimisation of desmopressin, and no specific therapy for COVID-19
- He was discharged after placement of a pacemaker

COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; IL-6, interleukin-6; LDH, lactate dehydrogenase; L-T4, L-thyroxine; RR, relative risk; SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus 2

Loli P, et al. Endocr Abstr. 2020;70:AEP1075

COVID-19 AND HYPOPITUITARISM
SELECTED CASES – SAN RAFFAELE HOSPITAL

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CASE #2

- A 78-year-old male patient with hypopituitarism after surgery for a suprasellar arachnoid cyst was on stable therapy with L-T4, cortisone acetate (25 mg/day), testosterone, and growth hormone
- Admitted to the ER with cough, dyspnoea, and fever for 1 week. He tested positive for SARS-CoV-2; chest CT showed COVID-19-associated pneumonia
- Mistakenly, cortisone acetate therapy was missed for 40 hours while in the ER. Blood tests showed hyponatraemia (Na^+ 129 mmol/L) and increased LDH (230 U/L) and CRP (53 mg/L)
- He received low-flux oxygen, ritonavir/lopinavir, and hydroxychloroquine. His clinical conditions significantly improved and he was discharged after 6 days

COVID-19, coronavirus disease 2019; CRP, C-reactive protein; CT, computerised tomography; ER, emergency room;
CRP, C-reactive protein; L-T4, L-thyroxine; LDH, lactate dehydrogenase; SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus 2
Loli P, et al. Endocrin Abstr. 2020;70:AEP1075

COVID-19 AND HYPOPITUITARISM
SELECTED CASES – SAN RAFFAELE HOSPITAL

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CASE #3

- An 18-year-old male with hypopituitarism after surgery for craniopharyngioma at 12 years of age, severe obesity (BMI 49.5), diabetes insipidus, was on stable therapy with L-T4, hydrocortisone (25 mg/day), desmopressin, testosterone, and rHGH
- He presented to the ER with fatigue and drowsiness and no respiratory symptoms. He tested positive for SARS-CoV-2. Chest X-rays showed an increased vascular pattern in both lungs. Blood tests showed increased CRP (25 mg/L), normal IL-6 and D-dimer
- He received antibiotic therapy and prophylactic anticoagulant coverage with LMWH; oral hydrocortisone was doubled. No respiratory complications occurred and the patient was discharged 3 days later

BMI, body mass index; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; ER, emergency room; IL-6, interleukin-6; LMWH, low-molecular-weight heparin; L-T4, L-thyroxine; rHGH, recombinant human growth hormone; SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus 2

Loli P, et al. Endocrin Abstr. 2020;70:AEP1075

COVID-19 AND HYPOPITUITARISM

- Patients with hypopituitarism do not seem to be protected from SARS-CoV-2 infection
- However, patients with hypopituitarism do not appear to be at an increased risk of developing more severe COVID-19
- Patients on active follow-up in a PTCOE are well aware of the possible risks related to infectious complications and know how to manage their own replacement therapy, when necessary

COVID-19, coronavirus disease 2019; PTCOE, Pituitary Tumour Centre of Excellence; SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus 2

Carosi G, et al. J Clin Endocrinol Metab. 2021;106:e1354–61; Loli P, et al. Endocr Abstr. 2020;70:AEP1075

COVID-19, VACCINATION, AND PITUITARY DISEASES/1

- In preparation for the upcoming COVID-19 vaccine, a survey of members of the Pituitary Society was conducted to understand planned approaches to glucocorticoid management in patients with adrenal insufficiency who will receive the vaccine
- The survey received 103 responses, including 36% who plan to recommend that patients automatically increase the glucocorticoid dosage with administration of the vaccine
- Of these, 84% plan to increase the glucocorticoid dose on the day of the vaccine, and 49% plan to increase the glucocorticoid dose prior to the vaccine

COVID-19, coronavirus disease 2019

Katznelson L, Gadelha M. Pituitary. 2021;24:143–5

COVID-19, VACCINATION, AND PITUITARY DISEASES/2

- In contrast, 64% plan not to automatically increase the glucocorticoid dose with vaccine administration. Of this group, 88% plan to increase the dose if the patient has a fever following administration, and 47% plan to increase the dose in the presence of myalgias and arthralgias

- Thus, most clinicians (64%), plan to maintain the current glucocorticoid dose with vaccine administration. The vast majority of such clinicians plan to increase the glucocorticoid dose with fever, and just over half the clinicians plan to increase the dose with associated arthralgias and myalgias, known side effects of the vaccine

COVID-19, coronavirus disease 2019
Katznelson L, Gadelha M. Pituitary. 2021;24:143–5

COVID-19, VACCINATION, AND PITUITARY DISEASES/3

- These data offer a glimpse into plans for glucocorticoid management in patients with adrenal insufficiency
- This survey does not reflect a trial on efficacy of glucocorticoid management in patients receiving the vaccine nor impact of a particular glucocorticoid dose on the immune response of the vaccine
- But, these data do offer suggested management guidance based on responses from experienced clinicians in pituitary diseases

CONCLUSIONS

- Involvement of the pituitary in COVID-19 is bidirectional
- COVID-19 can affect the gland directly or indirectly with pituitary apoplexy, SIADH, and hypophysitis being possible manifestations
- Management of pituitary functional adenomas is a challenge for endocrinologists and resulting syndrome may also predispose to COVID-19 incidence and severity
- Hypopituitary patients may be directly and indirectly exposed to SARS-CoV-2 infection and severe COVID-19 but, to date, have not shown increased severity of the disease
- Pituitary surgery has been impacted heavily by the COVID-19 environment
- Guidelines for vaccination of hypopituitary patients are lacking and careful surveillance is needed to offer guidance for a shared approach

COVID-19, coronavirus disease 2019; SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus 2;
SIADH, syndrome of inappropriate antidiuretic hormone secretion

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entire staff of the San Raffaele Scientific Institute,
for the extraordinary effort in the care of COVID-19 patients

In memory of the Italian workers who have given their lives
in the frontline fight against COVID-19

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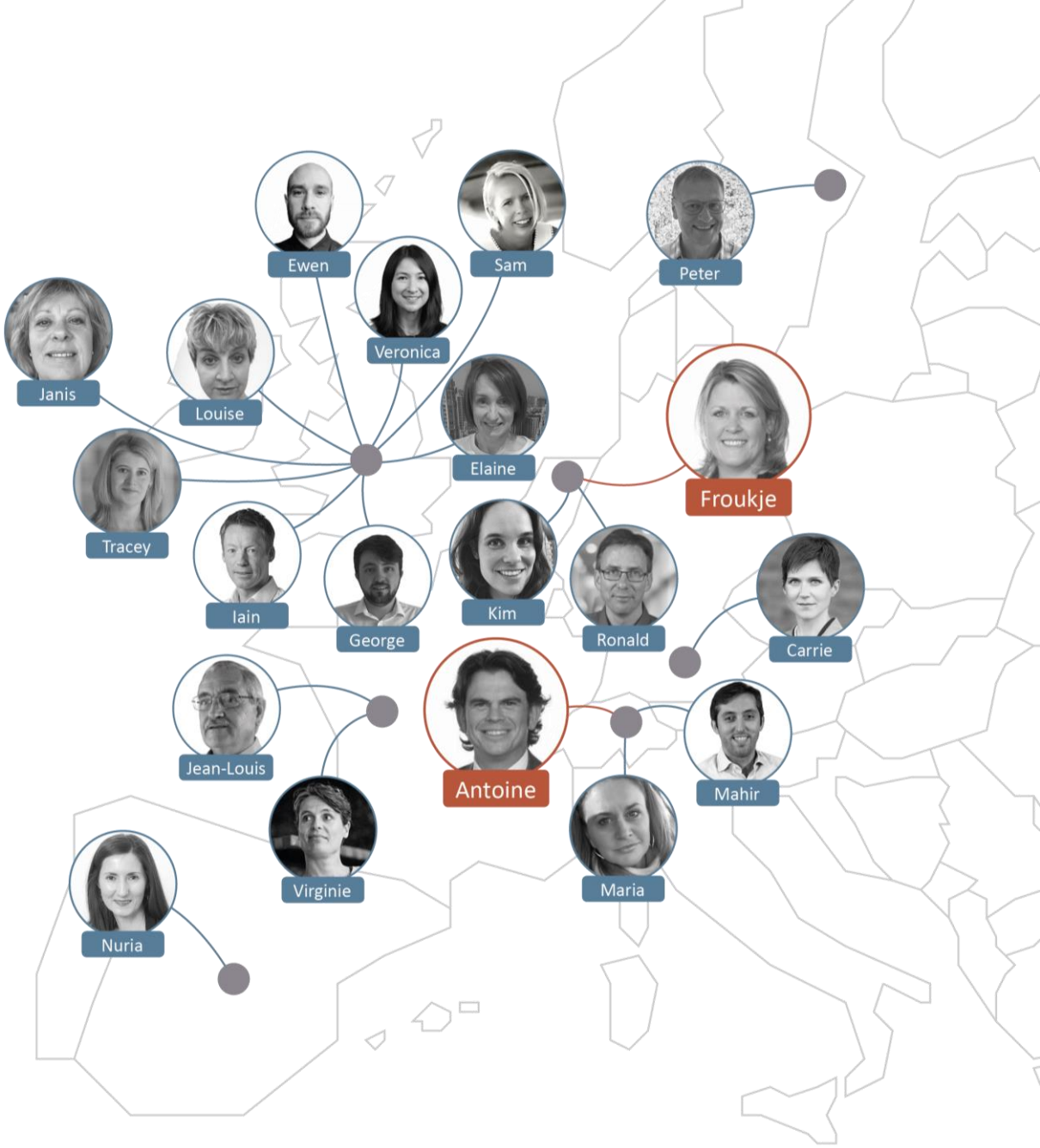

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