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RESEARCH

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Abstract

Background: Information on clinical outcomes of coronavirus disease 19 (COVID-19) infection in patients with adrenal disorders is scarce.
Methods: A collaboration between the European Society of Endocrinology (ESE) Rare Disease Committee and European Reference Network on Rare Endocrine Conditions via the European Registries for Rare Endocrine Conditions allowed the collection of data on 64 cases (57 adrenal insufficiency (AI), 7 Cushing's syndrome) that had been reported by 12 centres in 8 European countries between January 2020 and December 2021.
Results: Of all 64 patients, 23 were males and 41 females (13 of those children) with a median age of 37 and 51 years. In 45/57 (95%) AI cases, COVID-19 infection was confirmed by testing. Primary insufficiency was present in 45/57 patients; 19 were affected by Addison's disease, 19 by congenital adrenal hyperplasia and 7 by primary AI (PAI) due to other causes. The most relevant comorbidities were hypertension (12%), obesity (n = 14%) and diabetes mellitus (9%). An increase by a median of 2.0 (IQR 1.4) times the daily replacement dose was reported in 42 (74%) patients. Two patients were administered i.m. injection of 100 mg hydrocortisone, and 11/64 were admitted to the

Key Words

- adrenal insufficiency
- Cushing's syndrome
- glucocorticoids
- SARS-CoV-2

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hospital. Two patients had to be transferred to the intensive care unit, one with a fatal outcome. Four patients reported persistent SARS-CoV-2 infection, all others complete remission.

Conclusion: This European multicentre questionnaire is the first to collect data on the outcome of COVID-19 infection in patients with adrenal gland disorders. It suggests good clinical outcomes in case of duly dose adjustments and emphasizes the importance of patient education on sick day rules.

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Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic has reminded us that precautionary measures are important to protect the most vulnerable patient subgroups. The SARS-CoV-2 virus started to spread from Wuhan, China, in 2019, leading to a still ongoing pandemic. The virus is spread as a droplet infection. It mainly uses angiotensin-converting enzyme (ACE)-2 receptor for host cell entry in humans (1). Clinical manifestations can range from mild symptoms to a severe course of infection with pneumonia, acute respiratory distress syndrome (ARDS), hyperinflammation and cytokine storm, responsible for the high rate of hospitalizations and deaths (2, 3).

Besides the expression of ACE2 receptor and transmembrane protease serine 2 precursor co-receptor by the lung, gastrointestinal system and kidneys, these elements are also highly expressed in endocrine tissues, such as the hypothalamus–pituitary–adrenal axis (4). It was previously shown that SARS-CoV infection leads in about 40% of cases to the development of hypocortisolism, which might be caused by direct cytopathic effects of the virus itself or by immune mediators. This leads to the suggestion that based on the similarity of SARS-CoV-2 proteins to other SARS viruses, SARS-CoV-2 infections may potentially be prone to result in hypocortisolism (5). This might be caused by reversible hypophysitis or hypothalamic injury (6). Furthermore, thrombotic events at the adrenal level could also result in adrenal insufficiency (AI) (7). Another problem described in SARS-CoV is the molecular similarity of certain amino acid sequences of the virus itself with those of adrenocorticotropic hormone. It has been hypothesized that this could impair the normal stress-related cortisol rise by the interference of antibodies directed against those viral antigens with the host's natural secretion of corticosteroids (8). Recent studies in patients with SARS-CoV-2 infections confirmed significantly impaired adrenocortical function comparable to AI (9, 10). As in any other severe condition, critical illness-associated corticosteroid deficiency might also occur in severe SARS-CoV-2 infection (11). The use of corticosteroids for the treatment of patients with COVID-19 infection receiving oxygen or on invasive ventilation has shown to improve mortality rates most likely preventing cytokine storm and hyperinflammation (12, 13, 14, 15, 16).

Patients with preexisting adrenal gland disorders, such as AI and long-term glucocorticoid substitution therapy or glucocorticoid excess in Cushing's syndrome (CS), are regularly prone to infections, especially those of the upper airways and gastrointestinal tract, due to impaired immune cell function (17, 18). A small internal study of a single tertiary care centre in Lombardy, Italy, suggested a more than 5 times higher incidence of COVID-19 infection in a subgroup of 61 patients with Cushing's disease (CD) and 15 patients with active hypercortisolism compared to the general population, as well as a more severe clinical presentation, especially in patients with active hypercortisolism (19). However, these data were based on self-reported pulmonary infections during the period from January 2020 to April 2020, and only 2 patients in the study cohort of 122 patients had a confirmed and documented positive PCR test result.

An Italian retrospective case-control study evaluating the incidence of COVID-19 symptoms and complications in AI patients – hereby however counting suggestive COVID-19 symptoms, instead of positive PCR test results as confirmation of the disease – did not indicate a higher incidence of infections nor an increased disease severity compared to healthy controls (20). The risk of adrenal crisis (AC), however, persists in any infection including that with SARS-CoV-2 and might be even aggravated due to the virus's potential to cause hypocortisolism as described earlier. AC still is one of the most significant morbidity factors in AI with an incidence of 5–10 adrenal crises/100 patient years and a mortality rate of 0.5/100 years (21). In case of AC, quick diagnosis and correct treatment are essential (22). Therefore, optimal education of patients, relatives and attending physicians is the key factor to prevent or improve the outcome of AC (23).

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The aim of this European multicentre questionnaire was to gain further knowledge on the outcome of COVID-19 infection in these patient subgroups and to allow for better guidance during the ongoing pandemic.

Materials and methods

The e-reporting tool (e-REC) that has been developed as part of the European Registries for Rare Endocrine Conditions project was funded by the EU Health Programme (2014–2020) and supported by ENDO-ERN (European Reference Network on Rare Endocrine Conditions), European Society of Endocrinology (ESE) and European Society for Paediatric Endocrinology (ESPE) and is open to all centres across the world. Following a discussion with the ESE Rare Disease Committee in April 2020, this platform was extended for reporting COVID-19 infection in a patient with an existing rare endocrine or bone condition. Upon reporting a case, a unique ID was generated instantaneously for each case and emailed to users to be stored locally at the reporting centre. Reporters were invited to report any new case of COVID-19 infection in a patient with an existing adrenal disorder on a monthly basis and 'the reporting month' remained open for a period of 3 months. The reported data were stored on a secure server at the University of Glasgow and could be downloaded from the e-REC platform in MS Excel file format with details of the reporter, centre and information on the reported number of cases. No personally identifiable information was collected for the reported cases, and the process did not require informed patient consent. The project complied with EU GDPR and was approved by the Information Governance authorities at the NHS Greater Glasgow & Clyde Health Board and the National Research Ethics Service in the UK (REC Ref 17/WS/0178). Following notification of a case, the reporting clinician was invited to complete a clinical outcomes questionnaire to understand the natural history of the affected case.

Questionnaire design

The questionnaire was designed and distributed using Webropol (Valiant Office Suites, Valley Drive, Rugby, UK). Thirty-two questions were designed including a mixture of open questions and dichotomous or multiple-choice questions with either a single or multiple answer possibilities.

Study group

In total, 55 reference centres of EndoERN part of the main thematic group 'adrenal' (MTG1) were contacted to collect cases of COVID-19 infections in patients with adrenal disorders. Of these 55 centres, 12 centres (22%) of 7 different European countries supplied a total of 64 cases from January 2020 until December 2021.

Data extraction and analysis

Data extraction was performed using Microsoft Excel. Prism version 8 (GraphPad Software, Inc.) and Adobe Illustrator 24.3 2020 (Adobe) were used for statistical analysis and graphical presentation of the results.

Results

Characteristics of study cohort

Of all 64 cases of COVID-19 infection reported, 41 were female (median age 51.0 years (IQR 28.5)) and 23 were male (median age 37.0 years (IQR 41.0)). Adrenal gland disorders included in the questionnaire were AI (34 female, 23 male) and CS (7 female). Of AI patients, 25 female patients were affected by primary AI (PAI) including 14 patients with Addison's disease (AD), 9 with congenital adrenal hyperplasia (CAH) and 2 with other causes of PAI and 20 male patients (AD $n=5$, CAH $n=10$, other causes $n=5$), while 5 female patients and 2 male patient were affected by secondary AI and 4 female and 1 male patient by tertiary AI. Only seven female patients were suffering from CS, three of those due to CD and four patients due to adrenal hypercortisolism (Table 1).

Patients affected by autoimmune PAI presented with additional autoimmune diseases in 79% ($n=15$) of cases,

Table 1 Patient characteristics. Presentations of *n* and age as median age in years (interquartile range).

	Females ($n=41$)	Males ($n=23$)
Age	51.0 (28.5)	37.0 (41.0)
Adrenal gland disorders		
Adrenal insufficiency	34	23
Primary	25	20
Autoimmune	14	5
Congenital adrenal hyperplasia	9	10
Others	2	5
Secondary	5	2
Tertiary	4	1
Cushing's syndrome	7	0
Pituitary	3	-
Adrenal	4	-

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namely hypothyroidism ($n=11$, 58%), hypogonadism ($n=5$, 26%), diabetes mellitus type 1 ($n=2$, 11%), Graves' disease ($n=1$, 5%) and celiac disease ($n=1$, 5%) (Table 2).

Comorbidities were obesity (AI: $n=8/57$, 14%; CS: 5/7, 71%), hypertension (AI: $n=7/57$, 12%; CS: $n=3/7$, 43%), diabetes mellitus (AI: $n=4/57$, 9%; CS: $n=3/7$, 43%), malignancy (AI: $n=5/57$, 9%; CS: $n=1/7$, 14%), osteoporosis (AI: $n=2/57$, 4%; CS: $n=1/7$, 14%), heart disease (AI: $n=1/57$, 2%; CS: $n=2/7$, 29%), dyslipidemia (AI: $n=1/57$, 2%; CS: $n=1/7$, 14%), anemia (AI: $n=2/57$, 4%), pulmonary disease (CS: $n=1/7$, 14%), chronic kidney disease (CKD) (CS: $n=1/7$, 14%), rheumatoid arthritis (AI: $n=2/57$, 4%), common variable immunodeficiency (AI: $n=1/57$, 2%), Guillain Barré (AI: $n=1/57$, 2%) and anti-neutrophil cytoplasmatic antibody (ANCA) positive vasculitis (AI: $n=1/57$, 2%) (Table 3 and Fig. 1).

Mode of transmission of COVID-19 infection

Of all 64 patients with adrenal gland disorder and COVID-19 infection, 35 (55%) stated to have had known contact with other individuals who had been tested positive for COVID-19, while 27 (42%) were not aware of any risk contact. Two of the patients did not respond to the question.

Symptoms of patients with adrenal gland disorders and COVID-19 infection

Symptoms experienced during infection with coronavirus were fever (AI: $n=35/57$, 61%; CS: $n=5/7$, 71%), followed by tiredness or exhaustion (AI: $n=34/57$, 60%; CS: $n=2/7$, 29%), cough (AI: $n=29/57$, 51%; CS: $n=2/7$, 29%), muscle pain (AI: $n=27/57$, 47%; CS: $n=1/7$, 14%), headache (AI: $n=19/57$, 33%), the COVID-19 infection typical loss of taste and smell (AI: $n=15/57$, 26%; CS: $n=1/7$, 14%), sore throat (AI: $n=14/57$, 25%; CS: $n=1/7$, 14%), loss of appetite (AI: $n=15/57$, 26%), shortness of breath (AI: $n=11/57$, 19%), gastrointestinal symptoms (AI: $n=11/57$, 19%; CS: $n=2/7$, 29%) and a runny nose (AI: $n=10/57$, 18%). Of patients with AI, 10/57 experienced other symptoms not included in our list of answers. Six patients with AI reported being asymptomatic during the whole time of infection with COVID-19, three of those were patients with CAH (compare Fig. 2).

Dose adjustments of patients with glucocorticoid replacement therapy during COVID-19 infection

In total, 57 of 64 (89%) patients reported daily use of glucocorticoid replacement therapy, of which 44 were adult patients with adrenal gland disorders and 13 children between the age of 1 and 18 years (Fig. 3). Fludrocortisone replacement was used by 38 of 64 (59%) of patients, of which 12 were children. Of all patients with CAH, dose adjustments were used in 53% of cases with no use of emergency hydrocortisone injection. A daily glucocorticoid replacement dose (hydrocortisone equivalent) of 20.0 mg/day (IQR 5.0) was used in adult female patients, while 30.0 mg/day (IQR 15.0) were used by adult male patients with adrenal disorders. Of all 44 adult patients on glucocorticoid replacement therapy, 36 (82%) increased their daily replacement dose from a mean of 20.0 mg/day (IQR 5.0) in females and 30.0 mg/day (IQR 15.0) in males to a dose of 42.5 mg/day (IQR 22.5) in female and 50.0 mg/day (IQR 25.0) in male patients, respectively.

Regarding patients between the age of 1 and 18 years, female patients were substituted with a median daily dose of 8.0 (IQR 11.5) mg/day and male patients with a dose of 22.0 (IQR 19.0) mg/day. Of all 13 children with daily glucocorticoid replacement therapy, 6 (46%) increased their daily replacement dose from a median of 8.0 mg/day (IQR 11.5) in girls and 22.0 mg/day (IQR 19.0) in boys to a dose of 18.0 mg/day (25.0) in girls and 48.0 mg/day (32.0) in boys, respectively.

Table 2 Prevalence of other autoimmune diseases in patients with Addison's disease. Presentation of values as *n* (%) or directly in %.

Autoimmune disease	Prevalence in AD cohort ($n=19$)	Prevalence in previously published data (29)
Hypothyroidism	11 (58)	3.7–32
Hypogonadism	5 (26)	4.5–17.6
Diabetes mellitus type I	2 (11)	1.2–20.4
Grave's disease	1 (5)	2.0–22.7
Celiac disease	1 (5)	1.2–8

AD, Addison's disease.

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Table 3 Cormorbidites. Presentation of prevalence in %.

	Adrenal insufficiency		Cushing's syndrome	
Comorbidity	Prevalence in study cohort ($n = 57$)	Prevalence in previously published data (31, 32, 41)	Prevalence in study cohort ($n = 7$)	Prevalence in previously published data (30, 33)
Obesity	14	16	71	32–41
Hypertension	12	20–47	43	55–85
Diabetes mellitus	9	7–24	43	20–47
Malignancy	9	10–22	14	
Osteoporosis	4		14	22–57
Heart disease	2	19	29	25–93
Dyslipidemia	2	16–28	14	38–71
Anemia	4			
Pulmonary disease		12–27	14	
Chronic kindey disease		25–31	14	
Rheumatoid arthritis	4			
Common variable immunodeficiency	2			
Guillain Barré	2			
ANCA positive vasculitis	2			

Across all 42 patients with dose adjustments, this equals an increase by a median of 2.0 (IQR 1.4) times the original daily replacement dose.

Hospitalization of patients with adrenal gland disorders and COVID-19 infection

Despite dose adjustments as described earlier and two patients reporting the use of emergency glucocorticoid injection, four patients with AI ($n = 5/57$, 9%), of which two were patients with CAH, were admitted to the hospital due to AC and four because of the severity of COVID-19 infection ($n = 4/57$, 7%). Of the seven patients with CD, 43% ($n = 3/7$) were hospitalized due to the severity of COVID-19 infection. Overall, two patients had to be treated in the intensive care unit (ICU) with a length of stay (LOS) of 30–37 days of admission, while the median LOS in normal wards was 7.0 days. Patients hospitalized because of AC presented with a LOS of 1–5 days, while patients hospitalized because of severe infection stayed for 7–15 days in normal wards. Of those 11 patients hospitalized, 8 had previously adjusted their daily dose of glucocorticoid therapy. In total, the length of hospitalization was insignificantly lower in the subgroup of patients with dose adjustments compared to those without the use of emergency adjustment (median 8 (IQR 22.25) vs median 11 (IQR 11), $P = 0.8242$). However, due to low sample size, this does not allow us to conclude

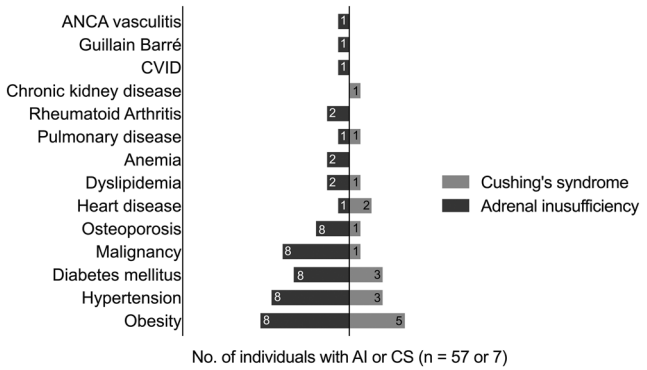

Figure 1
Comorbidities of patients with adrenal gland disorders. Bar chart depicting the absolute number of patients with adrenal insufficiency in black ($n = 57$) or Cushing's syndrome in grey ($n = 7$) presenting with coexisting comorbidities. Most prevalent comorbibities were obesity with eight or five patients, respectively, followed by hypertension, diabetes and malignancy.

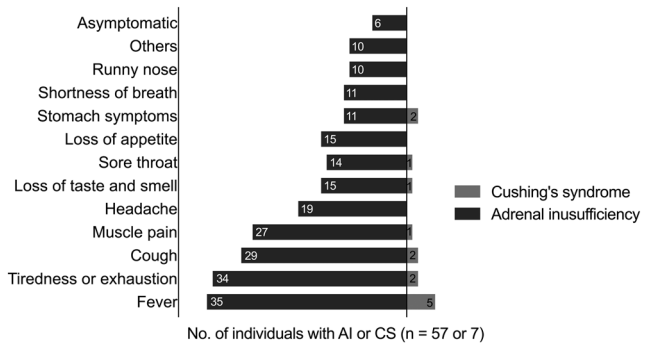

Figure 2
Symptoms of patients with COVID-19 infection and underlying adrenal gland disorder. Bar chart depicting the absolute number of patients with adrenal insufficiency in black ($n = 57$) or Cushing's syndrome in grey ($n = 7$) presenting with characteristic symptoms of COVID-19 infection, such as fever, tiredness or exhaustion, cough, muscle pain, headaches and the typical loss of taste and smell in COVID-19 infections.

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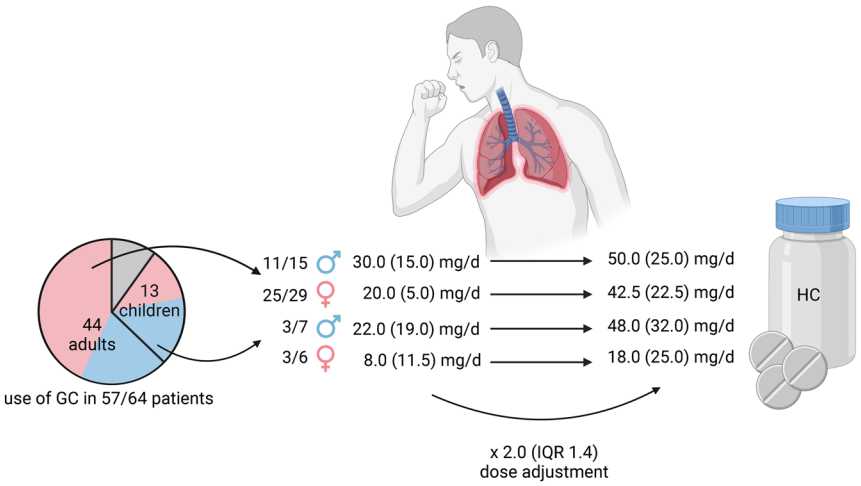

Figure 3
Dose adjustments of patients with glucocorticoid replacement therapy. Glucocorticoid (GC) replacement therapy with hydrocortisone (HC) was used by 57 (44 adults and 13 children) of 64 patients. Pink is used to illustrate female patients and blue for male patients. Arrows link normal daily median (IQR) replacement dose and final median (IQR) daily dose after dose adjustment. Included is also the median factor (IQR) of dose adjustment.

that dose adaption is not relevant for the course and severity of the disease. Hospital admission only occurred in adults ≥ 37 years and the mean age of patients that had to be hospitalized because of either severity of infection or AC was 55 years (Fig. 4).

Outcome of COVID-19 infection in patients with adrenal gland disorders

Of all 64 patients with adrenal gland disorders and COVID-19 infection, 59 (92%) patients reported complete remission of the disease, while 4 patients (6%) reported persistent disease and 1 patient (2%) suffered from lethal outcome (Fig. 4). The patient with fatal outcome was a 60-year-old female patient with CD on treatment with ketoconazole with multiple comorbidities (hypertension, obesity, diabetes mellitus, heart disease, chronic obstructive pulmonary disease (COPD), CKD and malignancy). The patient had to be admitted to the hospital due to the severity of the infection and passed away after 30 days of ICU treatment. Patients with CAH showed the highest rate of remission (89%) with only two patients reporting the persistence of COVID-19 symptoms.

Discussion

This is to our knowledge the first multicentre analysis of course and outcome of COVID-19 infection in patients with adrenal gland disorders.

Regarding the study cohort, most patients with AI were included. Patients with CS represented the minority of participants. Distribution of causes of PAI in our study cohort is mostly representative of the global PAI population (27, 28). The prevalence of correlating autoimmune disease in patients with autoimmune AD was comparable to previously published data (29), although the prevalence of hypothyroidism due to Hashimoto's thyroiditis was nearly twice as high in our study population (Table 2).

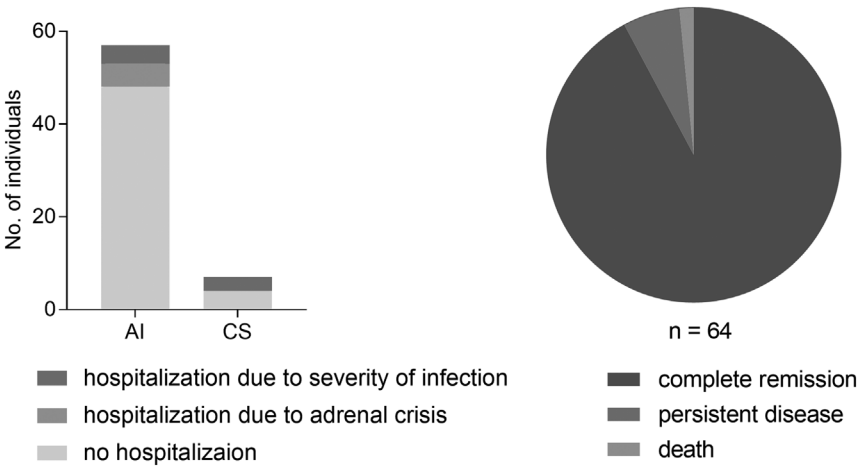

Figure 4
Hospitalization of patients with adrenal disorders and outcome of COVID-19 infection. (A) Bar chart displaying the causes of hospitalization in adrenal insufficiency (AI) and Cushing's syndrome (CS) patients with COVID-19 infection. Absolute numbers are depicted. (B) Pie chart illustrating the outcome of COVID-19 infection in the whole study population ($n = 64$).

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Most frequent comorbidities in patients with adrenal gland disorders are hypertension, obesity, diabetes, heart disease and dyslipidemia (30, 31, 32, 33). The prevalence of comorbidities in our study cohort of patients with AI and CS was comparable (Table 3). The most common comorbidities were obesity, hypertension and diabetes in both types of adrenal gland disorders, which are some of the major risk factors for a severe course of infection of COVID-19 disease (34, 35, 36). In our analysis, more than half of all patients stated to have had known risk contact and all patients had received a positive PCR-test result to confirm infection. Although our small study cohort of 55 patients with adrenal gland disorders seems to be quite representative of the global population in terms of patient characteristics, the data obtained are most probably influenced by selection bias, as only tertiary care centres with expertise in the field of adrenal gland disorders participated. A further disadvantage of the chosen study outline is a lacking healthy control cohort as well as information on the number of individuals with adrenal gland disorders treated at the respective centres with no history of SARS-CoV-2 infection.

Symptoms of patients with COVID-19 infection can vary from mild respiratory-infection-like symptoms to severe sepsis-like disease progression and ARDS (2). Cardinal symptoms of infection described in a systematic review and meta-analysis of 148 studies from 9 different countries, including 24,410 adults with confirmed COVID-19 infection were fever with a prevalence of 78%, followed by a dry cough with 58% and fatigue in 31% of cases (37). As these were also the symptoms most prevalent in our study cohort, our data appear to be conclusive and an existing adrenal condition does not seem to influence symptoms experienced during COVID-19 infection.

Moreover, a 7% rate of hospitalization of patients with AI was comparable to previously published data on the rate of hospitalization in the general population. The majority of infections has been reported as uncomplicated with 5–10% of patients hospitalized due to pneumonia or severe inflammation and respiratory dysfunction (38). Of patients with AI, 9%, however, had to be hospitalized due to AC resulting in a nearly twice as high total rate of hospitalization of patients with AI compared to the general population. Keeping in mind the nearly exponential rise in the incidence of COVID-19 hospitalizations with age (39), it was interesting to see that despite the risk of AC in the subgroup of AI patients, there were no hospital admissions reported in the age group of <35 years. The youngest patient submitted to the hospital because of AC was 37 years of age and the mean age of patients that had to be hospitalized because of either severity of infection or AC was 55 years vs a mean age of 65 years during the first and second wave in a Turkish study (40). Differences in the mean age of hospitalization, however, have to be interpreted cautiously, as not only the criteria for hospitalization markedly changed during the different waves of infection but also the development of vaccinations, different medication and the evolution of further variants influenced the age of hospitalization and outcome of the disease. Although with such a small cohort of seven patients with CS included in our study indicating a high possibility of selection bias, hospitalization rates were clearly elevated in CS patients with 43% of patients hospitalized because of the severity of COVID-19 infection. These data clearly support our initial hypothesis of CS patients being likely to be prone to severe course of infection due to the high incidence of comorbidities with a known negative impact on the outcome of infection.

Compared to the current global mortality rate per absolute number of cases varying between 0.5 and 6% depending on the individual country, the observed case–fatality ratio in our study population of patients with AI and CS does not seem to be elevated. As expected, the one case with fatal outcome included in our study refers to a 60-year-old female patient with CD with several comorbidities including hypertension, obesity, diabetes mellitus, heart disease, COPD, CKD and malignancy. Compared to LOS in cases of hospitalization due to COVID-19 described in the general population with a median of 5 (IQR 3–9) days and ICU LOS of approximately 7 (IQR 4–11) days, length of hospitalization in our study cohort was definitely longer, especially in the cohort hospitalized because of the severity of infection, most likely owing to the high chance of illness related complications, such as prolonged infection or bacterial and fungal superinfections as a result of impaired immune function.

Patients with CAH made use of dose adjustments in only 53% of cases, however, showed the highest rate of remission of 89%, most likely to differences in the pathophysiology of PAI.

Daily dose adjustments upon infection with SARS-CoV-2 were however only performed by 82% of adult patients and an even lower rate of 46% of children. This low rate of dose adjustments in children can easily be explained by asymptomatic courses of infection in the rest of the cases. Our data confirm that most patients followed the known standards of use of emergency

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glucocorticoid medication by doubling or tripling the usual daily glucocorticoid dose in cases of fever and other COVID-19-related symptoms. These guidelines on the prevention and management of AI during the global COVID-19 pandemic have been provided by the European and Italian Society of Endocrinology. In case of acute COVID-19 infection with fever or cough, oral stress doses of 20 mg hydrocortisone should be taken every 6 h. In case of further clinical deterioration, they advised immediate emergency injection of 100 mg hydrocortisone intramuscularly and continuous i.v. infusion of 200 mg hydrocortisone per 24 h (24, 25, 26). Stringent social distancing, possession of a 'steroid emergency card' and sufficient glucocorticoid supplies including emergency preparations for oral and systemic use were advised (24). In our study, the use of emergency hydrocortisone injection was described in 2 of 64 cases, which appears to be relatively low in comparison to 11 cases of hospitalization in our study cohort. Although it did not seem to influence the final disease outcome, it highlights that even in our preselected subgroup of patients treated at experienced endocrine tertiary care centres with expertise in adrenal gland disorders, knowledge and especially patients' confidence in the implementation of stress dosing is still to be further improved.

To conclude, despite elevated rates of hospitalization due to either potential occurrence of AC or multimorbidity in patients with CS also resulting in increased hospital LOS, our study suggests good clinical outcomes in case of duly dose adjustments and emphasizes the importance of patient education on sick day rules.

Declaration of interest

All authors have declared that no conflict of interest exists.

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