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Increased risk of hospitalization, intensive care and death due to COVID-19 in patients with adrenal insufficiency: A Swedish nationwide study

Ragnhildur Bergthorsdottir[1,2], Daniela Esposito[1,2], Daniel S Olsson[1,2,3], Oskar Ragnarsson[1,2,4], Per Dahlqvist[5], Sophie Bensing[6,7], Jonatan Nåtman[8], Gudmundur Johannsson[1,2] & Fredrik Nyberg[9]

From the [1]Department of Internal Medicine and Clinical Nutrition, Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden; [2]Department of Endocrinology, Sahlgrenska University Hospital, Gothenburg, Sweden; [3]Cardiovascular, Renal and Metabolism (CVRM), BioPharmaceuticals R&D, AstraZeneca, Gothenburg, Sweden; [4]Wallenberg Center for Molecular and Translational Medicine, University of Gothenburg, Gothenburg, Sweden; [5]Department of Public Health and Clinical Medicine, Umeå University, Umeå, Sweden; [6]Department of Molecular Medicine and Surgery, Karolinska Institutet, Stockholm, Sweden; [7]Department of Endocrinology, Karolinska University Hospital Stockholm, Sollentuna, Sweden; [8]Centre of Registers Västra Götaland, Gothenburg, Sweden; and [9]School of Public Health and Community Medicine, Institute of Medicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden

Abstract. Bergthorsdottir R, Esposito D, Olsson DS, Ragnarsson O, Dahlqvist P, Bensing S, et al. Increased risk of hospitalization, intensive care and death due to COVID-19 in patients with adrenal insufficiency: A Swedish nationwide study. *J Intern Med.* 2023;**00**:1–9.

Background. Patients with adrenal insufficiency (AI) have excess morbidity and mortality related to infectious disorders. Whether patients with AI have increased morbidity and mortality from COVID-19 is unknown.

Methods. In this linked Swedish national register-based cohort study, patients with primary and secondary AI diagnosis were identified and followed from 1 January 2020 to 28 February 2021. They were compared with a control cohort from the general population matched 10:1 for age and sex. The following COVID-19 outcomes were studied: incidence of COVID-19 infection, rates of hospitalization, intensive care admission and death. Hazard ratios (HR) with 95% confidence intervals (95% CI) adjusted for socioeconomic factors and comorbidities were estimated using Cox regression analysis.

Results. We identified 5430 patients with AI and 54,300 matched controls: There were 47.6% women, mean age was 57.1 (standard deviation 18.1) years, and the frequency of COVID-19 infection was similar, but the frequency of hospitalization (2.1% vs. 0.8%), intensive care (0.3% vs. 0.1%) and death (0.8% vs. 0.2%) for COVID-19 was higher in AI patients than matched controls. After adjustment for socioeconomic factors and comorbidities, the HR (95% CI) was increased for hospitalization (1.96, 1.59–2.43), intensive care admission (2.76, 1.49–5.09) and death (2.29, 1.60–3.28).

Conclusion. Patients with AI have a similar incidence of COVID-19 infection to a matched control population, but a more than twofold increased risk of developing a severe infection or a fatal outcome. They should therefore be prioritized for vaccination, antiviral therapy and other appropriate treatment to mitigate hospitalization and death.

Keywords: adrenal insufficiency, COVID-19, glucocorticoids, hospitalization, intensive care, death

Introduction

Adrenal insufficiency (AI) is a rare condition with inadequately low cortisol production. Primary AI (PAI) is caused by disorders of the adrenal gland, whereas secondary AI (SAI) is due to a hypothalamic-pituitary disease disrupting the secretion of adrenocorticotropic hormone. Patients with AI are dependent on daily replacement therapy with glucocorticoids (GCs) that needs to be increased during physical stress, such as during an infection with fever, in order to avoid a life-threatening adrenal crisis [1, 2].

Patients with AI have an increased overall morbidity and mortality rate, mainly from infectious and cardiovascular diseases [3–7]. A compromised natural killer cell function, weakening the innate immune system, has been shown in patients with PAI, which could partly explain why they are more prone to certain infections and have a more severe outcome [8]. GC replacement therapy in patients with AI cannot fully mimic normal GC exposure and normal diurnal rhythm, which may result in an unfavourable metabolic state, the suppression of the immune system and an adverse pro-inflammatory profile, possibly making patients with AI more susceptible to severe infections [9, 10]. This is supported by studies showing that patients with AI are prescribed more antimicrobial agents and that they are at increased risk of hospitalization due to infections [11, 12]. Altogether, infections constitute a major threat and challenge to patients with AI.

COVID-19 is caused by the SARS-CoV-2 coronavirus. The clinical spectrum of COVID-19 ranges widely from asymptomatic or mild respiratory illness to severe pneumonia that may have a fatal outcome [13]. Older age, male sex and cardiometabolic comorbidities such as hypertension, diabetes mellitus and cardiovascular disease are major determinants of poor prognosis and death due to COVID-19 [14]. As patients with AI have excess morbidity and mortality related to infectious diseases in general, it is likely that they are a risk group for more severe COVID-19 infection.

Data on outcome following COVID-19 infections in patients with AI are sparse due to the rarity of the disorder, and evidence is limited by small sample sizes, heterogeneity in terms of study designs and a general lack of matched control groups [15–22]. The aim of this study was therefore to investigate the risk of contracting COVID-19, as well as the risk of hospital admission, intensive care and death due to COVID-19, in a nationwide unselected cohort of patients with AI.

Methods

The study received ethical approval from the Swedish Ethics Review Authority, no. 2020-01800, with subsequent amendments. It is a Swedish nationwide register-based cohort study based on the SCIFI-PEARL (Swedish COVID-19 Investigation for Future Insights – A Population Epidemiology Approach Using Register Linkage) project, with a regularly updated database of multiple linked registers and healthcare databases. SCIFI-PEARL has the capability to identify various COVID-19 outcomes over time: It originally included all individuals in Sweden diagnosed with COVID-19 and a large general population comparison cohort, as described elsewhere [23], but was later extended to the entire Swedish population from 1 January 2015.

Data for the current study were obtained through the linkage of data from several national registers included in SCIFI-PEARL: (1) the SmiNet national register of notifiable communicable diseases to identify individuals testing positive for COVID-19; (2) the Swedish National Patient Register (NPR) to identify patients with PAI and SAI, patients hospitalized for COVID-19 disease and comorbidities among study subjects based on specialist inpatient and outpatient care; (3) the Swedish Intensive Care Register (SIR) to identify patients who were admitted to intensive care for COVID-19; (4) the National Diabetes Register (NDR) to identify diabetes mellitus in study subjects; (5) the Cause-of-Death Register (CoDR) to identify the time and cause of death, including COVID-19 deaths; (6) the National Prescribed Drug Register (NPDR) to identify patients on long-term GC treatment as well as other medical treatments of interest in the study subjects; (7) the National Register of the Total Population; (8) the Statistics Sweden Longitudinal Integrated Database for Health Insurance and Labour Market Studies for data on socio-demographic factors and (9) the National Vaccination Register for data on time, dose and type of COVID-19 vaccination.

Subjects included had to be 18–95 years of age and resident in Sweden on the index date (1 January 2020). Patients with AI were identified among the study population based on hospitalizations or specialist care visits in the NPR during the 5 years prior to the index date (2015–2019) for at least one of the following diagnoses as a primary or secondary diagnosis coded according to the International Classification of Diseases, tenth revision (ICD-10): E27.1 (primary adrenocortical insufficiency); E27.2 (Addisonian crisis); E25.0 (congenital adrenogenital disorders associated with enzyme deficiency); E23.0 (hypopituitarism); E89.3 (postprocedural hypopituitarism) or E31.0 (autoimmune polyglandular failure). To ensure high accuracy in patient selection, an oral GC (Anatomical Therapeutic Chemical [ATC] code H02AB, oral drug formulations) had to be

dispensed at least twice according to the NPDR during the year prior to index date. Exclusion criteria were the following diagnoses: E27.3 (drug-induced adrenocortical insufficiency); E27.4 (other and unspecified adrenocortical insufficiency); E71.3 (adrenoleukodystrophy) or E24 (Cushing's syndrome) registered either as a primary or secondary diagnosis from specialist in- or outpatient care in the NPR during 2015–2019. For some analyses, the AI group was subdivided into SAI (ICD-10 codes E23.0 or E89.3) or PAI (E27.1 or E25.0).

A reference population was selected that did not have any AI diagnosis (see definition of the AI cohort above). These controls were matched 10:1 based on year of birth and sex (Fig. S1, appendix p 6).

Five COVID-19 outcomes were studied. *Test positive for COVID-19 infection* was defined as the first positive PCR test result for SARS-CoV-2 in the SmiNet register. *COVID-19 infection diagnosis* was defined as the first of the following: a positive test result for SARS-CoV-2 in SmiNet, or a specialist visit or hospitalization with COVID-19 (ICD-10 code U07.1 or U07.2) as primary or secondary diagnosis in the NPR or as underlying or contributing cause of death in the CoDR. Hospitalization for COVID-19 was the first hospitalization for COVID-19 (ICD-10 code U07.1 or U07.2) as primary or secondary diagnosis in the NPR. Intensive care unit (ICU) admission for COVID-19 was defined as the first ICU admission for COVID-19 (ICD-10 code U07.1 or U07.2) as primary or secondary diagnosis in the SIR register. Finally, COVID-19 death was defined as a death registered with ICD-10 code U07.1 or U07.2 as underlying or contributing cause of death in the CoDR.

The different COVID-19 outcomes were all analysed separately. For each outcome, all subjects were followed from the index date (1 January 2020) until the earliest event for the specific outcome or emigration, death or end of study period (28 February 2021).

Descriptive baseline variables and covariates included comorbidities defined as a primary or secondary diagnosis from the NPR in 2015–2019 for the following conditions: ischaemic heart disease (ICD-10 codes I20–I25); other heart disease (atrial fibrillation, heart failure and atherosclerosis; I48, I50, I70); cerebrovascular disease (I61–I64); hypertensive disease (I10–I15); chronic lower respiratory disease (J43–J46) and diabetes mellitus (E10 or E11 in the NPR or a registration in the NDR in 2015–2019). Education was classified in three levels based on the highest education obtained: primary, secondary or tertiary/university. Gross salary income was used for income. Marital status was defined as married/registered partner or not married (including divorced or widowed). GC and mineralocorticoid use in the AI patients was captured from the NPDR in 2019 for the different oral corticosteroids used in Sweden (ATC codes H02AB or H02AA with subcodes, oral formulations). Vaccination status at end of follow-up, the duration of hospital stay (days) for patients who were hospitalized and admitted to ICU and the place of death (at home, nursing home or hospital) were also obtained and are presented descriptively.

Descriptive statistics are presented as number and proportion for categorical variables and mean and standard deviation (SD) for continuous variables. To be able to assess the distribution of baseline variables of different types and magnitude or prevalence between the cohorts, the standardized mean difference (SMD) was used. Larger SMD means larger difference (greater imbalance) between the cohorts, with values ≤ 0.2 indicating reasonable balance.

Cox proportional hazards analyses were performed to evaluate the five COVID-19 outcomes for AI patients compared to the matched control cohort with adjustments for a range of confounders including sex and age (through matching), education, income, marital status, ischaemic heart disease, other heart disease, cerebrovascular disease, hypertensive disease, chronic lower respiratory disease and diabetes mellitus. We estimated both crude (unadjusted) and adjusted hazard ratios (HRs) with 95% confidence intervals (CIs). Due to missing data on socioeconomic variables, 115 AI patients and 1224 controls (2.2% of the study population) were not included in the adjusted HR analysis. We also performed an analysis of effect modification stratified by sex, and two sensitivity analyses excluding patients with diabetes, and censoring vaccinated patients at vaccination, respectively [24–26].

Role of the funding source

The funders for this academic investigator-initiated study played no role in the conception of the study,

Table 1. *Patients with adrenal insufficiency (AI) in the Swedish population on 1 January 2020 by diagnoses registered 2015–2019 in the National Patient Register (NPR).*

	ICD-10 code	No. of patients[a]
AI diagnosis		
Primary adrenocortical insufficiency	E27.1	2098
Addisonian crisis	E27.2	279
Autoimmune polyglandular failure	E31.0	144
Congenital adrenal disorders associated with enzyme deficiency	E25.0	360
Hypopituitarism	E23.0	3111
Postprocedural hypopituitarism	E89.3	0
Total		5430

Abbreviations: AI, adrenal insufficiency; ICD-10, International Classification of Diseases, tenth revision.
[a]Patients may have more than one AI diagnosis code in their register-based medical history.

its design, data collection, analysis or interpretation, or writing or revision of this manuscript.

Results

Description of the study cohorts

A total of 5430 patients with AI were included in the study (Table 1): 2584 (47.6%) were women, and the mean age was 57.1 (SD 18.1) years (Table 2). The majority of patients were treated with hydrocortisone ($n = 4695$, 86.5%), and the uses of other GCs were considerably less frequent. A total of 1503 patients (77.2%) of the PAI cohort were prescribed mineralocorticoid treatment with fludrocortisone, the only mineralocorticoid marketed in Sweden (Table 2). The frequency of diabetes, hypertension and chronic lower respiratory disease was higher in AI patients than in the age- and sex-matched controls (Table 2), but COVID-19 vaccination status was relatively similar during follow-up (1 dose [11.6% vs. 8.2%] and 2 doses [6.2% vs. 4.4%], respectively; appendix p 2). The durations of hospital and ICU stays were also similar between the cohorts (Table S1, appendix p 2). Of the 177 deaths, a total of 106 (59.9%) occurred during hospitalization, 54 (30.5%) in nursing homes, and 17 (9.6%) at home in a private residence or at an unknown location: The proportions were quite similar in the two cohorts. Deceased AI patients and controls due to COVID-19 were older and had a higher prevalence of cardiovascular and cerebrovascular diseases than those who were alive at the end of the follow-up (Table S2, appendix p 3).

COVID-19 infection, hospitalization and death

During follow-up, a test-positive COVID-19 infection was found in 375 (6.9%) AI patients and 3395 (6.3%) controls, and a COVID-19 infection diagnosis as defined (positive test or not) was registered for 410 (7.6%) AI patients and 3501 (6.4%) controls (Fig. 1). During the study period 116 (2.1%), AI patients were hospitalized for COVID-19 and 15 (0.3%) required intensive care compared to 455 (0.8%) and 44 (0.1%) of the controls, respectively (Fig. 1). The crude HR for hospitalization and intensive care for COVID-19 was 2.59 (2.11–3.18) and 3.44 (1.92–6.19), respectively. After adjustment for socioeconomic factors and comorbidities, the adjusted HR was 1.96 (1.59–2.43) for hospitalization and 2.76 (1.49–5.09) for intensive care admission (Fig. 1).

Regarding mortality, 43 (0.8%) patients with AI died with COVID-19 as a registered underlying or contributing cause during the study period compared with 134 (0.2%) in the control cohort. Thus, crude and adjusted HR (95% CI) for death from COVID-19 were 3.25 (2.30–4.58) and 2.29 (1.60–3.28) times higher for AI patients than controls, respectively (Fig. 1).

In the sex-stratified analysis, the AI-related risks were not significantly different for men and women. The sensitivity analyses excluding subjects with diabetes (type 1 or 2) or censoring subjects who had received their first dose of COVID-19 vaccine did not change the analysis results or conclusions of the study (Table S3, appendix p 4).

SAI and PAI subgroup analysis

There were 2936 patients with SAI and 1948 patients with PAI. Mean (SD) age was higher in the SAI patients than those with PAI: 60.0 (17.9) versus 53.3 (17.8) years. In addition, the proportion of men was higher among SAI patients (60.2 %) (Table 2). The frequencies of hospitalization (2.4% vs. 1.6%), intensive care (0.4% vs. 0.1%) and death (1.2% vs. 0.3%) for COVID-19 were numerically higher in patients with SAI than PAI (Table S4, appendix p 5).

Table 2. *Baseline characteristics on 1 January 2020 in patients with adrenal insufficiency (AI) and their age- and sex-matched controls from the Swedish national population and subdivided by patients with primary AI (PAI) and secondary AI (SAI).*

	AI patients (n = 5430)	Controls (n = 54 300)	SMD	PAI[b] (n = 1948)	SAI[b] (n = 2936)	SMD
Age	57.1 (18.1)	57.1 (18.1)	<0.001	53.3 (17.8)	60.0 (17.9)	0.378
Women	2584 (47.6)	25840 (47.6)	<0.001	1077 (55.3)	1169 (39.8)	0.314
Glucocorticoid prescription[a]						
Hydrocortisone	4695 (86.5)	31 (0.1)	3.563	1715 (88.0)	2464 (83.9)	0.119
Fludrocortisone	1874 (34.5)	13 (0.0)	1.025	1503 (77.2)	24 (0.8)	2.514
Prednisolone	897 (16.5)	3134 (5.8)	0.347	352 (18.1)	490 (16.7)	0.036
Betamethasone	403 (7.4)	2023 (3.7)	0.162	104 (5.3)	276 (9.4)	0.156
Dexamethasone	19 (0.3)	36 (0.1)	0.062	10 (0.5)	9 (0.3)	0.032
Prednisone	15 (0.3)	35 (0.1)	0.051	2 (0.1)	12 (0.4)	0.061
Methylprednisolone	2 (0.0)	4 (0.0)	0.020	0	0	N/A
Concurrent diseases						
Ischaemic heart disease	356 (6.6)	2766 (5.1)	0.062	86 (4.4)	235 (8.0)	0.149
Other heart disease	547 (10.1)	3617 (6.7)	0.123	134 (6.9)	353 (12.0)	0.177
Cerebrovascular disease	182 (3.4)	910 (1.7)	0.107	29 (1.5)	132 (4.5)	0.177
Diabetes, type 1 or 2	941 (17.3)	5275 (9.7)	0.224	330 (16.9)	467 (15.9)	0.028
Hypertension	1484 (27.3)	7688 (14.2)	0.329	392 (20.1)	940 (32.0)	0.273
Chronic lower respiratory disease	469 (8.6)	1868 (3.4)	0.219	139 (7.1)	278 (9.5)	0.085

Note: Data are n (%) or mean (SD).
Abbreviations: AI, adrenal insufficiency; ICD-10, International Classification of Diseases, tenth revision; N/A, not applicable; PAI, primary adrenal insufficiency; SAI, secondary adrenal insufficiency; SMD, standardised mean difference.
[a]Some patients received different glucocorticoids so percentages do not add up to 100%.
[b]PAI and SAI are defined as ICD-10 codes E27.1 or E25.0, and E23.0 or E89.3, respectively.

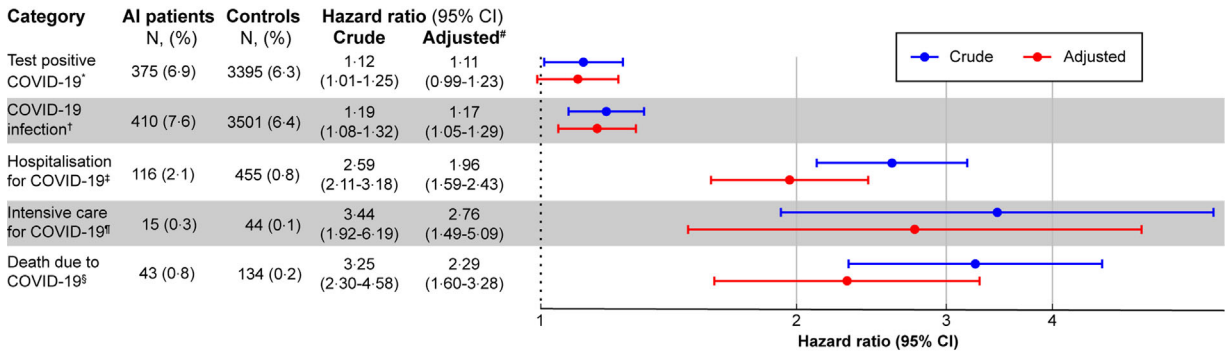

Fig. 1 *Hazard ratios for COVID-19 infection, severe disease and death. Comparison of COVID-19 outcomes in patients with adrenal insufficiency and matched controls (crude and adjusted) during follow-up from 1 January 2020 to 28 February 2021. AI, adrenal insufficiency; CI, confidence interval. ICD-10, International Classification of Diseases, tenth revision; ICU, intensive care unit; n, number; PCR, polymerase chain reaction. *First positive PCR test result for SARS-CoV-2 in the SmiNet Register. †First ICD-10 code (U07.1 or U07.2) as primary or secondary diagnosis in the Swedish National Patient Register (NPR) or the Cause-of-Death Register (CoDR), or positive test result for SARS-CoV-2 in the SmiNet register. ‡First hospitalization for COVID-19 (ICD-10 code U07.1 or U07.2) as primary or secondary diagnosis in the NPR. ¶First ICU admission for COVID-19 (ICD-10 code U07.1 or U07.2) in the Swedish intensive Care Register (SIR). §ICD-10 code U07.1 or U07.2 as the underlying or contributing cause of death in the CoDR. #Adjusted for socioeconomic factors and comorbidities.*

Discussion

This is the first nationwide population-based study investigating the risk of COVID-19 and the course of the disease in patients with AI compared with a matched cohort from the general population. The study shows that patients with AI have a more than doubled risk of hospitalization, need for intensive care and death from COVID-19. This study therefore adds AI as an important risk factor for death due to COVID-19 disease.

Our study, based on a nationwide unselected population of patients with AI and a large, matched control population, shows markedly increased morbidity and mortality due to COVID-19 even after adjustment for comorbidities such as hypertension and diabetes mellitus. There are very few studies on the outcome of patients with AI and COVID-19 during the pandemic. Eight cross-sectional studies have described self-reported outcome in patients with AI during suspected COVID-19 infection [15–22]. One of the studies, which included patients with benign pituitary lesions without AI as controls, reported no difference between patients with AI compared with patients without AI with respect to symptoms or hospitalization at the start of the pandemic [15]. Three of the studies showed that psychological well-being was negatively affected by the pandemic [16, 17, 19]. One multinational survey reported increased incidence and increased hospitalization for COVID-19 among AI patients compared with the global population, with older age, male sex, congenital adrenal hyperplasia and higher GC replacement doses being associated with worse outcome [18]. A Swedish multicentre questionnaire survey including 615 patients with autoimmune Addison's disease showed that 17% of the cohort contracted COVID-19, but few of the patients needed hospitalization [20]. These previous studies are limited by small numbers of patients and the lack of a matched control group. Furthermore, in four of the studies, important clinical confounders known to be associated with worse outcome of COVID-19 were not reported [15, 16, 19, 22].

Oral hydrocortisone is the most commonly used GC for replacement treatment for AI in Europe [27–29], consistent with the 86.5% of the AI patients found in our study cohort. Antihypertensive treatment and diabetes mellitus are known to be more prevalent among patients with AI (both PAI and SAI), and higher GC replacement doses in patients with SAI are also associated with an adverse metabolic profile [6, 10, 11, 30, 31]. Indeed, in the current study, we also found diabetes mellitus, hypertension and chronic respiratory disease to be more prevalent among patients with AI than in the controls, even after matching for sex and age. However, after adjustment for these confounding factors, the increased risk for developing severe COVID-19 disease and death still remained, indicating that AI per se, or its treatment, is related to a more severe outcome.

Studies on health outcome and mortality in patients with AI are challenging, as AI is a rare condition. Therefore, in order to obtain statistical power, pooled analysis for both PAI and SAI was performed. Although both groups have AI and depend on GC replacement therapy, their underlying condition and comorbidities differ, which should be considered when interpreting the results. A sub-analysis for PAI and SAI was performed, indicating that patients with SAI may be more severely affected by COVID-19 than patients with PAI. However, as there were differences in age and comorbidities between the two groups, these results should be interpreted with caution (Table S4, appendix p 5).

The risk of adrenal crisis during an infectious disease is clinically very important in patients with AI [3–6, 8, 11, 12], even if they have been adequately educated in steroid-emergency treatment [32, 33]. Awareness of the elevated risk of adrenal crisis during a COVID-19 infection among patients and healthcare professionals might explain the increased rate of hospitalization in patients with AI but does not explain increased admission to intensive care and death due to COVID-19. The clinical definition of adrenal crisis is not well established, and the ICD-10 diagnostic code for adrenal crisis (E27.2) is neither validated nor used consistently as cause of death. Therefore, it was not possible to determine if adrenal crises specifically contributed to the adverse outcome in patients with AI. The incidence of test-confirmed or overall diagnosed COVID-19 infection among patients with AI was not higher than in controls, which argues against both increased susceptibility to COVID-19 infection and excessive testing among the patients. Another important factor that may have affected the outcome in the opposite direction is the fact that patients with AI may have isolated themselves to greater extent than

the controls to avoid COVID-19; however, a lower COVID-19 incidence might then be expected in the AI patients, which was not the case.

The current study describes the natural course of COVID-19 in most of the patients, as the study period mainly covers the time before vaccination for SARS-CoV-2 (vaccination in Sweden started on 27 December, 2021 for the elderly and some high-risk groups). This is supported by the low and similar vaccination status among AI patients and controls by the end of the study period (Table S1, appendix p 2). It should also be noted that neither the Delta nor Omicron waves had emerged as data were only available until February 2021.

A major strength of this study is the use of an unselected national study cohort comprising both patients with AI and matched population controls. The health registers in Sweden hold comprehensive data on all individuals, including patients with this rare disease, and the search strategy used to identify AI patients has been previously used successfully and is thought to be reliable, reflecting the known prevalence of AI in Sweden [11]. The controls, selected from the whole Swedish population, were carefully matched for age and sex, and socioeconomic status and comorbidities were adjusted for in the outcome analysis. Another strength of this study is the national coverage of the information on COVID-19 testing, and its outcome and vaccination status. Limitations that should be acknowledged are the lack of detailed clinical data such as body mass index, clinical observation during admission to inpatient care and intensive care, and the lack of actual doses of GC replacement in the patient population as well as information on adrenal crisis and GC treatment during inpatient management.

In conclusion, we find that patients with AI have an increased risk for severe and fatal COVID-19 infection and should therefore be prioritized for vaccination and other preventive measures. Furthermore, patients and healthcare professionals should be vigilant for signs or symptoms to ensure early diagnosis of COVID-19 so that patients can be recommended adequate GC "stress treatment" and other appropriate treatment in time to prevent hospitalization and death.

Author contributions

The study was designed by all the authors. Data were collected, and statistical analysis was performed by Fredrik Nyberg and Jonatan Nåtman, who have directly accessed and verified the underlying data reported in the manuscript. All the authors participated in the analysis and interpretation of the data. Ragnhildur Bergthorsdottir and Fredrik Nyberg supervised the research activity, and Ragnhildur Bergthorsdottir prepared and created the initial draft of the manuscript with the remaining authors. Daniela Esposito, Daniel S Olsson, Oskar Ragnarsson, Per Dahlqvist, Sophie Bensing, Jonatan Nåtman, Gudmundur Johannsson and Fredrik Nyberg also contributed to writing and revision of the manuscript. All authors reviewed and approved the submitted manuscript. All authors made the decision to submit the manuscript for publication, meet the International Committee of Medical Journal Editors criteria about authorship and take full responsibility for integrity, accuracy and completeness of the data.

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Conflict of interest statement

DSO has been a consultant for Ipsen and Pfizer, has received unrestricted grants from Sandoz and Pfizer and is an employee at AstraZeneca as of August 8 2021. GJ has served as a consultant for Novo Nordisk, Shire and AstraZeneca and has received lecture fees from Novo Nordisk and Pfizer AB. DE has received lecture fees from Pfizer and Ipsen. FN owns some AstraZeneca shares. RB reports no personal fees but has been or is a site investigator for Takeda, Pfizer and Shire at Sahlgrenska University Hospital. OR, PD, SB and JN have nothing to declare.

Data availability statement

The data in this study are deidentified (pseudonymized) individual-level data from Swedish healthcare registers and can be obtained from the respective Swedish public data holders on the basis of ethics approval for the research in question, subject to relevant legislation, processes and data protection.

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Correspondence: Ragnhildur Bergthorsdottir, Department of Endocrinology, Sahlgrenska University Hospital, Blå stråket 5, 413 45 Gothenburg, Sweden.
(Email: ragnhildur.bergthorsdottir@medic.gu.se).

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supporting information ■