Adrenal insufficiency at the time of COVID-19: a retrospective study in patients referring to a tertiary centre.

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Adrenal insufficiency and COVID-19

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Abstract

Context. COVID-19 represents a global health emergency and infected patients with chronic diseases often present with a severe impairment. Adrenal insufficiency (AI) is supposed to be associated with an increased infection risk which could trigger an adrenal crisis.

Objective. Our primary aim was to evaluate the incidence of COVID-19 symptoms and complications in AI patients.

Design and setting. We conducted a retrospective case-control study. All patients were on active follow-up and lived in Lombardy, one of the most affected areas.

Patients. We enrolled 279 patients with primary and secondary AI and 112 controls (patients with benign pituitary lesions without hormonal alterations). All AI patients had been previously trained to modify their replacement therapy on stress doses.

Intervention. By administering a standardized questionnaire by phone, we collected data on COVID-19 suggestive symptoms and consequences.

Results. In February-April 2020, the prevalence of symptomatic patients (complaining at least one symptom of viral infection) was similar between the two groups (24% in AI and 22.3% in controls, p 0.79). Highly suggestive COVID-19 symptoms (at least two including fever and/or cough) also occurred equally in AI and controls (12.5% in both groups). No patient required hospitalization and no adrenal crisis was reported. Few nasopharyngeal swabs were performed (n=12) as indicated by sanitary regulations, limiting conclusions on the exact infection rate (two positive results in AI and none in controls, p 0.52).

Conclusions. AI patients who are adequately treated and trained, seem to display the same incidence of COVID-19 suggestive symptoms and disease severity as controls.

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Introduction

COVID-19 is an infectious respiratory syndrome caused by a novel coronavirus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (1). It has been firstly identified in Wuhan, China, as responsible for numerous pneumonia cases at the end of 2019. The infection has now spread worldwide, becoming a global health emergency (2). In Italy, Lombardy was the most hardly hit region by the pandemic and is still one of the most affected regions in the world, with a prevalence of swab-confirmed infection of 0.75% at the end of April (3). However, in Lombardy pharyngeal swab has been mostly performed in severely symptomatic patients referring to Emergency Rooms, thus the true prevalence of the disease is unknown. The estimated prevalence of infected people based on clinical manifestations, as in early April 2020, is 19.6% (4).

The clinical presentation of symptomatic infection from SARS-CoV-2 ranges from mild to critical. Most infections are mild, however, the 14% and 5% of patients show a severe and critical disease, respectively (5–11). In Italy, an overall fatality rate of 13.7 % has been registered, ranging from 0.2% in young patients to 31.7% in the elderly (3). The main symptoms reported in affected patients were fever, cough, myalgia or fatigue and dyspnea while minor symptoms included headache gastrointestinal symptoms and conjunctivitis (12).

Risk factors for severe illness are represented by advanced age, smoking, and several comorbidities such as cardiovascular disease, diabetes mellitus, chronic lung disease, cancer, chronic kidney disease, and obesity (12–17). Immunocompromising conditions and liver disease were proposed as potential risk factors although specific data are limited (18). Investigations about COVID-19 presentation in specific fragile groups with other chronic diseases have been started (19).

Adrenal insufficiency (AI) is a chronic condition of inadequate cortisol production from different origins (20). As reported by a recent statement released by the European Society of Endocrinology, patients with

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primary (PAI), mainly Addison's disease (AD), as well as secondary adrenal insufficiency (SAI), should be considered at risk of being affected by COVID-19 (21,22). Firstly, because of the overall increased risk of infections reported in AI patients (23), probably as a consequence of their inefficient innate immune response (24), and secondly, because of the increased mortality rate observed facing respiratory infections, mainly linked to adrenal crisis exacerbations (25). Some clinical guidelines on how to manage AI patients at the time of COVID-19 pandemic have been issued (22,26,27). However, so far, data on COVID-19 presentation and outcome in adrenal insufficient subjects are lacking.

Materials and methods

Study design and participants

We conducted an observational case-control study involving adult patients with chronic adrenal insufficiency, both primary (PAI) and secondary (SAI). As control group, we recruited patients with non-functioning pituitary microadenomas (NFPA) and empty sella, without hormonal deficiencies. We made this choice because we expected, in this group, the same incidence of infective diseases as normal subjects and, moreover, most anamnestic data were already present in medical records, avoiding the need for a protracted recruitment phase. Hypoadrenal patients with a previous diagnosis of Cushing syndrome have been excluded from the enrolment considering hypercortisolism a condition highly associated with an increased infection risk which may persist after surgical treatment (28). Patients with 21-hydroxylase deficiency were excluded too, on the basis of the potential role of hyperandrogenism on the severity of COVID-19 presentation (29–31).

Diagnosis of PAI and SAI was previously performed following International Guidelines (32,33). Other pituitary deficiencies in SAI patients, if present, were adequately replaced with specific hormonal therapies.

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Inclusion criteria for both groups were represented by an active follow up at our Endocrinology Unit, Ospedale Maggiore Policlinico, in Milan (last visit on site performed in the last two years) and by a stable residence in Lombardy region.

All patients' medical records sorted by name in our Centre were systematically analysed, and we extracted all patients presenting the cited inclusion criteria. All patients answered the phone call.

Methods

From 1st to 15th May 2020, we retrospectively collected clinical data using phone calls, asking patients to report any symptoms of viral infection that occurred from January 1st to April 30th 2020 and any specific exam performed. According to Italian epidemiological data on COVID-19 outbreak, (34) we considered as suggestive for SARS-CoV-2 infection only symptoms occurred from February 14th.

We registered the presence of fever (higher than 37.5 °C), cough, myalgia, fatigue, dyspnea, gastrointestinal symptoms, conjunctivitis, anosmia, ageusia, upper respiratory tracts symptoms, or others (thoracic pain, headaches, otalgia), along with the need to increase oral replacement therapy dosage or parenteral administrations of steroids. We collected data on nasopharyngeal swabs and chest imaging results. In the absence of swab and imaging data, we considered highly suggestive (HS) of COVID-19 patients reporting at least two symptoms including fever or cough which are the most frequent. We also analysed data defining HS-symptoms with stricter criteria, including the presence of at least two out of three of the cardinal symptoms: fever, cough and loss of sense of smell and/or taste. Hospitalization and emergency unit access for suspicious/confirmed COVID-19 infection were also registered.

Data on contacts with infected people, flu shot injection in the winter season, and smoking habits were collected. Working habits acquired from February were also collected.

Personal data (age and sex), cause of adrenal insufficiency, presence of pituitary deficiencies other than SAI, and the type of replacement therapy were extracted from patients' medical records.

All AI patients have been contacted at the start of pandemic receiving a brief reminder about keeping adherence to their replacement therapy and adopting sick day rules when indicated. We also invited patients to strictly observe national sanitary rules at work.

The Local Ethical Committee (Fondazione IRCCS Ca' Granda, Milan) approved the protocol study and patients gave their verbal consent to participate.

Statistical methods

All categorical data, including diagnosis of COVID-19 and suggestive symptoms, were expressed as percentage (%) and proportion (/) and analysed using Chi-squared test or Fisher exact test when indicated. Continuous parameters with normal distribution were described as mean ± standard deviation (SD) and compared using T test while non-Gaussian data were expressed using the median and the interquartile range (IQR) and compared using a non-parametric test (Wilcoxon-Mann-Whitney). Assuming that patients with hypoadrenalism showed a higher incidence of infections than the general population (we considered a RR of 2.5) (23), we estimated that at least 102 patients per group needed to be enrolled to detect a significant difference in COVID-19 incidence (with an alpha error of 5% and power of 90%). P-values <0.05 were considered as statistically significant. All statistical analyses were performed using SPSS, version 26 (IBM, Cary, NC, USA).

Results

Population characteristics

On the basis of inclusion criteria, we enrolled 279 AI patients: 219 SAI and 60 PAI with a mean age 57.5±15.6 and 56.8±15.7, respectively (p 0.754). AI females were 139/279 (49.8%) with a higher prevalence in PAI than SAI (68.3% vs 44.7%, respectively, p 0.001).

The SAI group included 86/219 (39.3%) patients with NFPA, 49/219 (22.4%) with functioning adenomas (29 acromegaly, 16 macro-prolactinomas, and four TSH-omas), 47/219 (21.5%) with various pituitary neoplasms (mostly craniopharyngiomas and cystic lesions), 28/219 (12.8%) with other causes of hypopituitarism (mostly idiopathic and post-traumatic), and 9/219 (4.1%) with empty sella. Pituitary hormonal deficiencies, other than SAI, were present in 188/219 (85.8%). Patients with a diagnosis of acromegaly and prolactinoma were well-controlled or in disease remission at the time of investigation.

Among PAI, 47 patients were affected with AD and 13 patients with post-surgical hypoadrenalism; among AD patients, 33 were in the context of an autoimmune polyglandular syndrome type 2 (APS 2).

AI patients were treated with cortisone acetate (CO) in 79%, with hydrocortisone (HC) twice or thrice daily in 11.5%, and with modified release hydrocortisone (m-HC) once daily in 9.5%. A CO dose of 25 mg/die was largely used (92.7%) with higher doses in a few patients (7.3%). HC varies from 15 to 25 mg daily (mean daily dose: 20.7 mg) while m-HC dosage varies from 15 to 25 mg daily (mean daily dose 21.1 mg daily).

In the control group, 112 patients were recruited (89 patients with NFPA and 23 with empty sella without hormonal alterations as inclusion criteria). Mean age was 57.5±14.3 and females were 52.7%.

AI and controls' characteristics (age, sex distribution, smoking, and working habits) were comparable, see Table 1. Only the prevalence of flu shots was higher in AI patents, as expected as a fragile group.

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COVID-19 suggestive symptoms and patients' management

Symptoms occurrence over time is displayed in Figure 1. In both AI and control groups, most patients reported the outset in March 2020 (38% and 36%, respectively). while another peak of symptoms was reported in controls in former February which overlaps with flu peak period (35) (21% *vs* 10% of symptomatic controls and AI respectively, p 0.096). Splitting the hypoadrenal group in symptomatic PAI and SAI, we confirmed that most patients in both groups complained their symptoms during COVID-19 outbreak (13% vs 21.5% in the second half of February, respectively, p=0.55 and 52% vs 32% in March, respectively, p=0.18).

As stated before, only symptoms that occurred from February 14th were considered as suggestive for COVID-19 and thus included in the following analysis of symptomatic patients.

The main clinical features and collected data of both AI patients and controls are shown in Table 1. The prevalence of symptomatic patients (complaining at least one symptom of viral infection, mentioned above) was similar between the two groups (24% in AI and 22.3% in controls, p 0.65). Specific symptoms distribution in the whole AI group, in SAI/PAI and in controls, is represented in Figure 2. Except for the higher prevalence of gastrointestinal symptoms in controls *vs* AI patients (42.3% *vs* 19.4%, respectively, p 0.03), no other differences between these groups were found. Comparing SAI and PAI, only fever prevalence was significantly higher in SAI *vs* PAI (60.5% vs 26.3% respectively, p 0.02).

The prevalence of HS-symptoms was equal in AI and controls (12.5%). Even considering stricter criteria, as defined in methods, the prevalence of HS-symptoms resulted once more similar (10.8 % in AI and 8.9 % in controls, p >0.99). A higher prevalence of HS-symptoms was observed in SAI than in PAI group, although not statistically significant (14.2% and 6.7%, respectively, p 0.19). Contacts with verified COVID-

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19 cases was also similar in AI and controls. HS-symptoms duration was unexpectedly longer in controls than AI (median 15 vs 7 respectively, p 0.04).

In 31.3% symptomatic AI patients, the replacement therapy dose was increased, especially in PAI group (47.4% in PAI and 25% in SAI, p 0.001). The increase was 1.5 fold the regular dose in 42.9% and two-fold in the others. Only one AD patient also practiced intramuscular hydrocortisone injections. Symptomatic patients who did not increase their replacement therapy reported only mild and rapidly improving symptoms. Moreover, most of patients did not consider symptoms as related to COVID-19 at the time of their occurrence. Antibiotics were prescribed by the general practitioner in 16.7% symptomatic AI patients and 20.8% controls (p 0.76). No patients required hospitalization and no adrenal crisis were reported.

In only 12/279 (4.3%) subjects, a nasopharyngeal swab for SARS-CoV-2 was performed (eight in AI patients and four in controls). In 8/12 cases, it was requested in the presence of HS-symptoms and in 4/12 because of contacts with COVID-19 patients. Two symptomatic AI patients were found to be positive and none in controls (p 0.52). Chest imaging was requested in two symptomatic controls (1.8%) and five AI (1.8%), showing a normal result in all patients. Overall, the occurrence of COVID-19 infection was thus confirmed in 0.7% of AI patients and 0% of controls (p 0.52), compared with 0.75% of the general population in Lombardy by the end of April (3).

We did not report any fatal event over the COVID-19 period (from February 14th – April 30th). One male patient, 79 years old, with acromegaly and SAI, died in early February (1/279, 0.36%). He was transported to the Emergency Unit in a comatose condition after several days of gastrointestinal symptoms, started on 20th January 2020. Few data are available on patient management at home on that occasion. Bedside lung ultrasound showed an A pattern excluding B lines which are typically encountered in COVID-19 infected patients. He displayed atrial fibrillation and echocardiography showed a severely dilated right atrium with an impaired systolic function. An acute neurologic event was also considered. Based on the

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time of symptoms occurrence and the clinical presentation, we deemed this event as not related to COVID-19.

Discussion

Adrenal insufficiency has been shown to be associated with increased infection risk and immunological alterations (23,24,36). These data mainly come from studies involving patients with PAI while no consistent data are available in SAI. It is well known that infections also represent the most frequent trigger for adrenal crisis which primarily contributes to the increased mortality rate reported in this group (25). Recently, some experts have remarked about the possible risk of COVID-19 contagion and complications in hypoadrenal patients, but the impact of the virus in this group has not been proved yet. Our specific investigation in this group pointed out some useful information.

According to our data, hypoadrenal patients appeared not to be exposed to a significantly higher risk of manifest COVID-19 typical symptoms than controls even if the exposure risk, based on contacts with infected people and working habits, seemed equal. Also, they did not display severe disease complications, without requiring hospital admissions. Along with that, no adrenal crisis was reported. No differences, even in mortality, have been found. Only one SAI patient died, but a relationship with SARS-CoV-2 infection was unlikely.

The study group included exclusively patients who were on active follow up in a dedicated tertiary endocrinological centre and thus, they have been highly instructed on the possible risks related to infections' complications and on how to manage their own replacement therapy, if necessary. These characteristics may have contributed to the similar clinical outcome we found in AI and controls.

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Epidemiological studies on COVID-19 in Italy reported a peak of notified cases in March which overlaps with the peak of suggestive symptoms we observed in both AI group and controls in that month (34). The other peak observed in former February, encountered in controls only, might be related to the seasonal flu virus peak (35). The higher number of flu shots in AI patients could explain this difference.

Unexpectedly we observed a longer duration of HS-symptoms in controls *vs* AI patients along with a higher prevalence of gastrointestinal symptoms. As previously stated, it is possible that AI patients, who are highly instructed on infectious diseases complications, adopted a safer behaviour, limiting their social contacts and applying better medical managing of virus-related symptoms. Moreover, we could speculate that the high prevalence of gastrointestinal symptoms observed in controls, which is in accordance to the 50% reported in recent studies, may be related to a release of the cytokine in the GI tract, a mechanism that could be mitigated by the steroids and by the inefficient innate immune response in IA patients (37).

The main study limitation is represented by the lack of certain diagnostic data on SARS-CoV-2 detection. According to sanitary regulations in Lombardy, nasopharyngeal swabs were performed in specific situations only, namely hospital admissions. The method of data collection, fully based on what patients reported on phone calls, is an additional important study limit. On the other hand, the major strengths are represented by the large number of AI patients recruited, the presence of a control population, and the absence of subjects who did not respond to the call, thus excluding the possibility to have missed hospitalized COVID-positive or dead patients. Future investigations, like serum SARS-CoV-2 antibodies evaluation, will be necessary to clarify the real infection rate in AI patients. A second limitation in our assessment is the incomplete knowledge base at the time of the interview that determined the questions we asked. However, except for cutaneous manifestations (39,40), all other signs and symptoms resulting today associated with COVID-19 were included (41). Lastly, we highlight that we decided to consider AI patients as a whole group in our main case-control analyses because, according to our statistical power analyses, the number of patients with PAI was limited.

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From our data, we can conclude that at the time of COVID-19 pandemic, patients with adrenal insufficiency who are adequately informed on infections related risks and who are adequately trained on replacement therapy self-adjustment, do not appear to be exposed to an increased risk of developing a more severe clinical impairment than controls.

Data Availability

Some datasets generated and analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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Legends

Table 1

Age is expressed as mean and range while symptoms duration as median and IQR (interquartile range).

PAI=primary adrenal insufficiency; SAI=secondary adrenal insufficiency; AI=adrenal insufficiency; p^1=p-value PAI vs SAI; p^2=p-value AI vs controls; CO=cortone acetate; HC=hydrocortisone; m-HC=modified release hydrocortisone; Symptomatic patients=patients presenting at least one suggestive symptom of viral infection; HS-symptoms=highly suggestive symptoms of COVID-19 (at least two including fever or cough); Contacts=direct contacts with infected people; * = p<0.05.

Figure 1

This Figure shows the distribution of symptomatic patients over time, from January to April 2020. We expressed, as a percentage, the ratio between patients who complained symptoms in a specific period and the total of symptomatic patients, in each group. Most patients, both in AI and controls, complained their suggestive symptoms during COVID-19 outbreak, especially on March 2020.

AI, patients with adrenal insufficiency; PAI, primary adrenal insufficiency; SAI, secondary adrenal insufficiency.

Figure 2

AI, adrenal insufficiency considered as a whole group; SAI secondary adrenal insufficiency; PAI, primary adrenal insufficiency; *, p<0.05 in controls vs AI; #, p<0.05 in SAI vs PAI; URTIS, upper respiratory tract infection symptoms; GIS, gastrointestinal symptoms;

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Table 1. Clinical features and collected data of AI patients and controls.

	PAI (n=60)	SAI (n=219)	p^1	AI (n=279)	Controls (n=112)	p^2
Age, years	56.8±15.7 (20-86)	57.5±15.6 (21-94)	0.75	57.3±15.6 (20-94)	57.5±14.3 (27-89)	0.96
Females, n (%)	41 (68.3)	98 (44.7)	0.001*	139 (49.8)	59 (52.7)	0.65
AI etiology, n (%)			-	-	-	-
Addison disease	47 (78.3)					
Adrenal surgery	13 (21.6)					
Pituitary neoplasms		182 (83.1)				
Other		49 (22.4)				
Replacement therapy						
CO, n (%)	34 (56.7)	187 (85.4)	<0.001*	221 (79)	-	-
HC, n (%)	13 (21.6)	19 (8.7)	0.01*	32 (11.5)		
m-HC, n (%)	13 (21.6)	13 (59.4)	0.0007*	26 (9.5)		
Smoking Habit, n (%)	5 (8.3)	38 (17.3)	0.10	43 (15.4)	21 (18.8)	0.45
Flu shot, n (%)	20 (33.3)	79 (36.1)	0.76	99 (35.6)	28 (25)	0.04*

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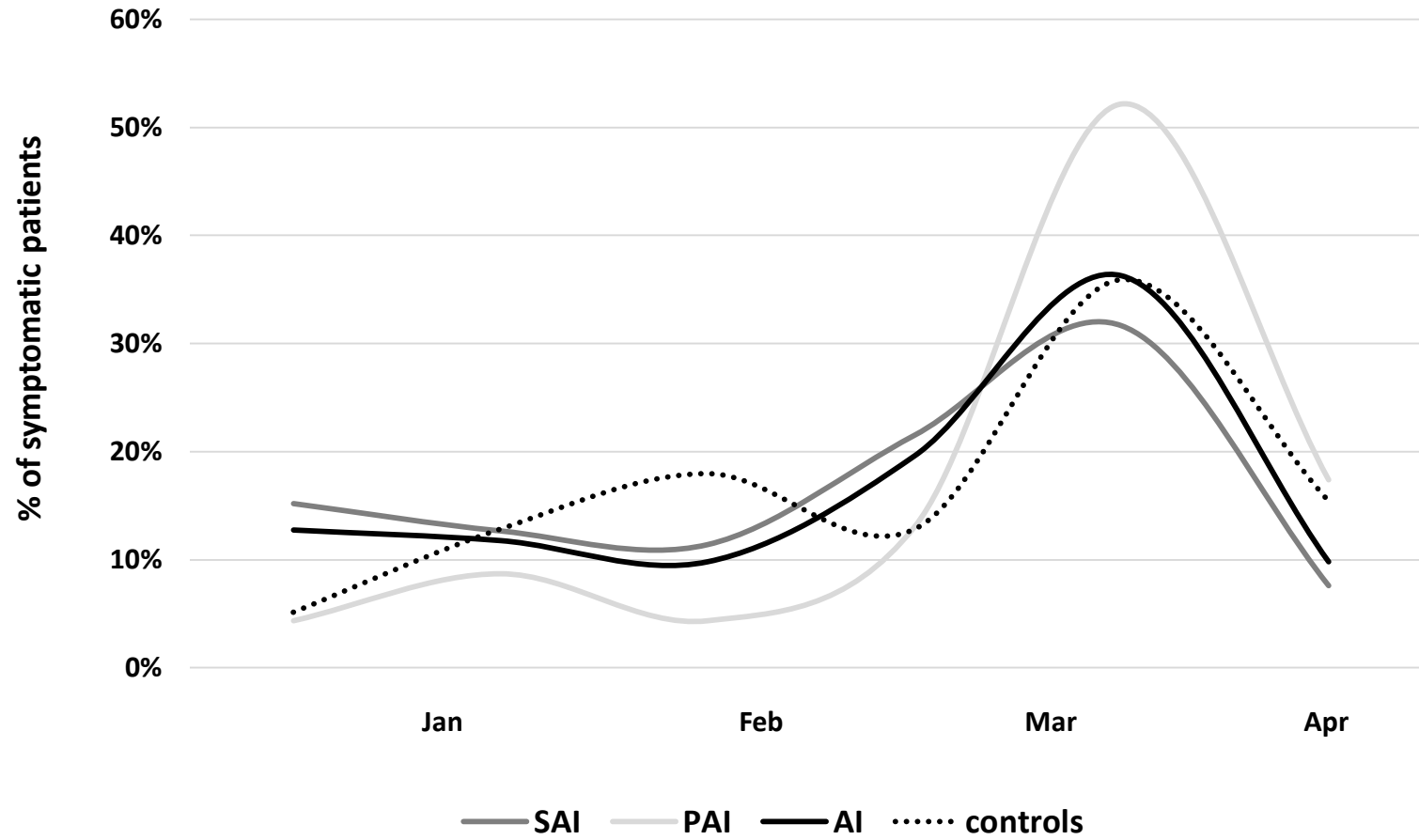|						
Symptomatic patients, n (%)	15 (25)	52 (23.7)	0.87	67 (24)	25 (22.3)	0.79
Symptoms duration, days	8.5 (3-19)	7 (3-15)	0.42	5 (3-15)	7 (3-15)	0.65
HS-Symptoms, n (%)	4 (6.7)	31 (14.2)	0.19	35 (12.5)	14 (12.5)	1.00
HS-Symptoms duration, days	14 (7-33)	7 (3-15)	0.14	7 (3-15)	15 (7-30)	0.04*
Active workers, n (%)	10 (16.7)	21 (9.6)	0.05*	31 (11.1)	13 (11.6)	0.86
High risk profession, n (%)	5 (8.3)	6 (2.7)	0.06	11 (3.9)	4 (3.6)	0.13
Contacts, n (%)	3 (5)	14 (6.4)	>0.999	17 (6.1)	6 (5.4)	1.00

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Figure 1
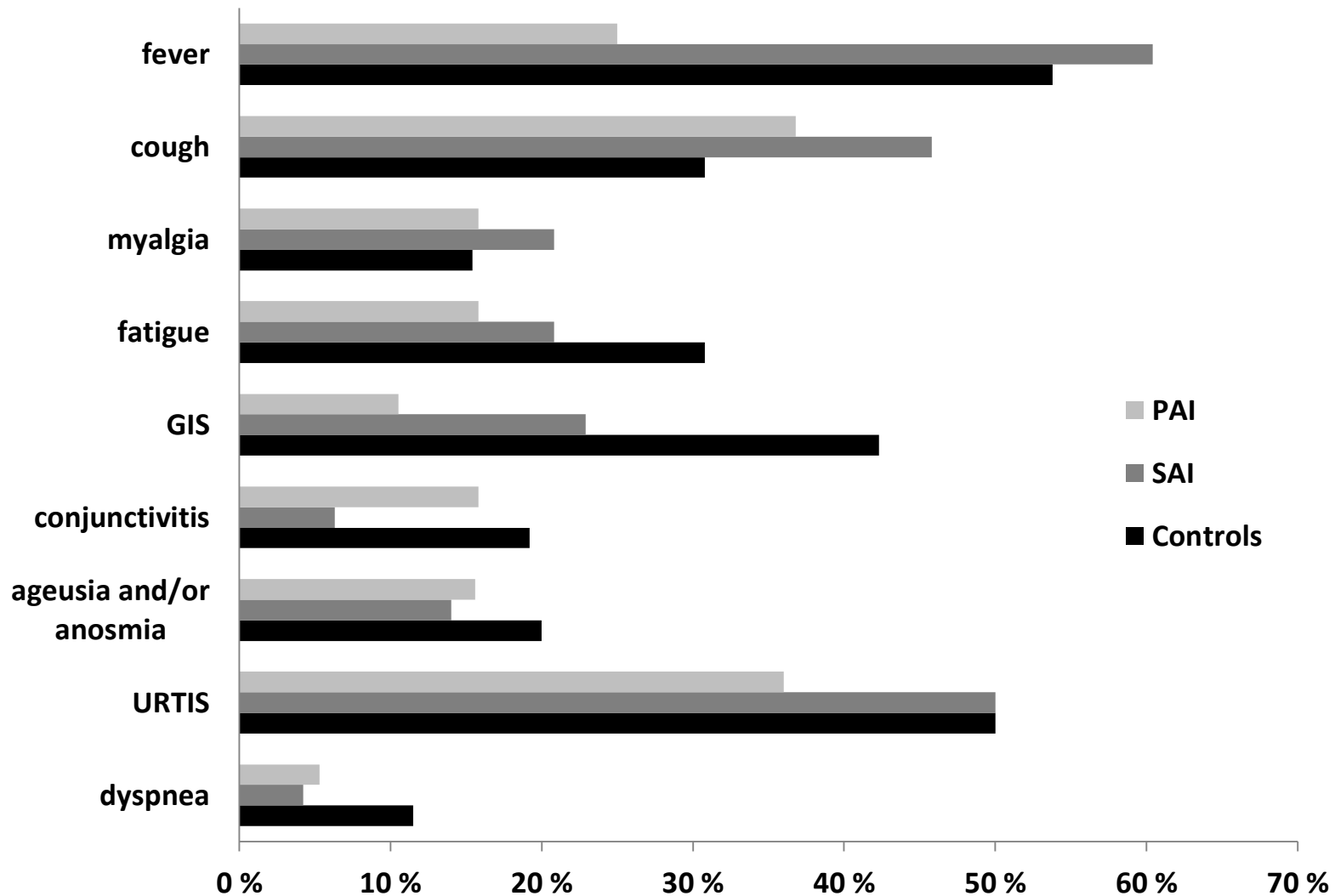Distribution of COVID-19 suggestive symptoms over time.

Figure 2 COVID-19 suggestive symptoms occurrence, expressed as percentage, in symptomatic hypoadrenal patients and controls.