Clinical Research Article

The Impact of the COVID-19 Pandemic on Self-Reported Outcomes in Patients With Adrenal Insufficiency

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Abbreviations: AI, adrenal insufficiency; CI, confidence interval; COVID-19, Coronavirus disease 2019; GIAI, glucocorticoid-induced adrenal insufficiency; HC, hydrocortisone; IQR, interquartile range; OR, odds ratio; PAI, primary adrenal insufficiency; SAI, secondary adrenal insufficiency.

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Abstract

Context: The COVID-19 pandemic has impacted healthcare environment.

Objective: To determine the impact of the pandemic on self-reported outcomes in patients with adrenal insufficiency (AI).

Design and setting: Prospective longitudinal survey study at 2 tertiary centers.

Participants: Patients with AI.

Intervention: Patient-centered questionnaire.

Main outcome measures: Depression Anxiety Stress Scales-21, Short Form-36, and AI self-management.

Results: Of 342 patients, 157 (46%) had primary AI, 109 (32%) had secondary AI, and 76 (22%) had glucocorticoid-induced AI. When compared to prepandemic, daily glucocorticoid dose and number of adrenal crises did not change. However, patients reported a higher financial impact from AI (34% vs 23%, \( P = 0.006 \)) and difficulty accessing medical care (31% vs 7%, \( P < 0.0001 \)) during the pandemic. A third of patients reported difficulty managing AI during the pandemic. After adjusting for duration and subtypes of AI, younger patients [odds ratio (OR) 2.3, CI 95% 1.3-4.1], women (OR 3.7, CI 95% 1.9-7.1), poor healthcare access (OR 4.2, CI 95% 2.3-7.7), lack of good insurance support (OR 2.8, CI 95% 1.3-5.9), and those with a higher financial impact (OR 2.3, CI 95% 1.3-4.3) reported greater difficulties managing AI. Patients were more likely to report a higher anxiety score (≥8) if they found managing AI challenging during the pandemic (OR 3.0,
Since March 2020, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the cause of coronavirus disease (COVID-19) has reached a pandemic level and become a global health emergency with high mortality and morbidity rates (1). As one of the severely affected countries, the United States had an estimated prevalence of infection of 7.9% and a positive case detection rate of 8.4% as of January 30, 2021 (2). Lockdown measures and social-distancing policy initially intended to control the spread of the virus led to inevitable social and economic impediment.

Adrenal insufficiency (AI) is an endocrine disorder characterized by adrenal cortical hormone deficiency and includes primary AI (PAI) and secondary AI (SAI) (3). Glucocorticoid-induced AI (GIAI) is a unique form of SAI caused by the chronic iatrogenic glucocorticoid use, leading to suppression of the hypothalamus-pituitary-adrenal axis (4). Patients with AI are susceptible to infections due to their inefficient innate immune system (5) and are prone to developing adrenal crises from insufficient hypothalamus-pituitary-adrenal axis activation in response to stressors (6).

Prior to the pandemic, multiple studies have demonstrated that despite standard hormone replacement therapy, patients with AI still experience a high burden of disease and report impaired quality of life (7-13).

To date, the evidence of optimal management of AI during the pandemic hinges on expert opinions from professional societies (14,15), with very scarce original data. One cross-sectional survey study of 279 patients conducted by phone in Lombardy, Italy, from February to April 2020, reported that patients with AI had similar prevalence of symptomatology suggestive of COVID-19 compared to controls, and no hospitalization or adrenal crisis was found (16). However, only a small proportion of the patients (4%) underwent COVID-19 confirmatory testing. Another cross-sectional survey study of 121 patients focusing on psychological stress, also in Italy from February to April 2020, reported a prevalence of COVID-19 infection as 0.8%, with patients’ concerns on personal health, finances, and quality of life (17). Both of the studies were limited by a small sample size, monocentric design within a single European country, assessment during the early stage of the pandemic, and lack of comparison to the prepandemic care.

We conducted the first longitudinal survey study during the COVID-19 pandemic in patients with AI enrolled in our prospective survey study at 2 tertiary medical centers in the United States. Our objective was to characterize the self-management, quality of life, and psychosocial measures of patients with AI and to determine the factors associated with difficulty with AI self-management, anxiety, and stress during the pandemic.

### Materials and Methods

#### Participants

The study protocol was approved by the institutional review boards at the 2 participating sites: Mayo Clinic (Rochester, MN, USA) and Brigham and Women’s Hospital (Boston, MA, USA). Patients with AI who were enrolled in the prospective longitudinal survey study at 2 tertiary centers as previously described (7) were contacted for interest and participation.

In total, 788 patients were sent an one-time COVID-19 supplemental survey in December 2020 by postal mail or by e-mail using a direct Research Electronic Data Capture (REDCap) link (18). At the time of survey administration and completion, COVID-19 vaccinations had not been available in the United States. Among 382 responders (48.5% response rate), 40 patients were excluded due to unclear diagnosis or reporting AI recovery, and 342 patients were included in the analysis [see Supplemental Figure 1 in (19)]. Among the final cohort, responses to a similar survey (without questions related to the COVID-19 pandemic) completed in January 2020 were identified and were available for paired analyses in 242 patients. Participants’ responses were linked to their medical records to verify diagnosis and treatment concordance, as well as relevant comorbidities. The verification procedures were similar at the 2 centers. We categorized AI into PAI, SAI, and GIAI. Reported glucocorticoids other than hydrocortisone (HC) were converted to HC equivalent: 1 mg prednisone and prednisolone as 4 mg HC, and 1 mg dexamethasone as 25 mg HC (20).

### Survey

The COVID-19 supplemental survey was constructed with input from coauthors. The questions included assessment of financial loss, job security, access to medical care, family support, and overall self-management during...
the pandemic. Mental health status was assessed with the Depression Anxiety Stress Scales-21; quality of life was re-assessed with the Short Form-36. The final version of the survey contained the following sections: the impact of the pandemic, quality of life during the pandemic, management of AI during the pandemic, COVID-19 infections, and feedback to study investigators [see supplemental appendix in (19)]. The term “adrenal crisis” in the survey referred to presentations to the emergency room to receive parenteral glucocorticoids.

Psychological Measures

The Depression, Anxiety and Stress Scales (DASS-21) were used to measure the prevalence and severity of depression, anxiety, and stress symptoms. This self-report scale consists of 21 items that comprise 3 subscales (7 items loading onto each subscale) measuring 3 symptom constructs—depression, anxiety, and stress. The DASS-21 has demonstrated good concurrent, convergent, and discriminant validity (21). All 3 subscales are considered to have excellent temporal stability and internal consistency in clinical samples. Cronbach’s alpha for the depression, anxiety, and stress subscales in clinical samples have been reported at 0.96, 0.89, and 0.93, respectively (17). The total depression subscale score was divided into normal (0-9), mild depression (10-13), moderate depression (14-20), severe depression (21-27), and extremely severe depression (28-42). The total anxiety subscale score was divided into normal (0-7), mild anxiety (8-9), moderate anxiety (10-14), severe anxiety (15-19), and extremely severe anxiety (20-42). The total stress subscale score was divided into normal (0-14), mild stress (15-18), moderate stress (19-25), severe stress (26-33), and extremely severe stress (34-42) (21).

Quality of Life Measures

The Short Form-36 (SF-36) is a self-assessment of quality of life over the previous four weeks in eight dimensions of health: physical functioning, role-physical limitation, bodily pain, general health, vitality, social functioning, role-emotional limitation, and mental health. In each domain, the range is 0 to 100, with higher scores indicating less pain or better functioning. Physical functioning, role-physical limitation, bodily pain, and general health may be merged in a comprehensive index for physical functioning (the Physical Component Summary), as well as vitality, social functioning, role-emotional limitation, and mental health may compose a comprehensive index of mental functioning (the Mental Component Summary). SF-36 summaries can be standardized to the US adult population (mean 50, SD 10), and higher scores indicate better health states. SF-36 scores within 5 points of the norm (45 to 55) are generally considered to be average or normative, whereas scores more than 10 points below the norm (<40) are indicative of significantly impaired health (22).

Statistical Analysis

Data from 2 participating sites were combined on January 30, 2021, and analyzed using the JMP software, version 14.1.0 (SAS Inc., Cary, NC, USA). Figures were generated with GraphPad Prism 8 (GraphPad Software, La Jolla, CA, USA). Variables were assessed for normality by the Kolmogorov-Smirnov test. Continuous variables were reported as mean and standard deviation or median and interquartile range (IQR) based on the distribution. Normative SF-36 data of 1998 US population were used to convert each score of 8 dimensions into decade- and sex-adjusted Z-score, as well as to calculate the Physical Component Summary and the Physical Component Summary (23). For continuous variables, comparisons between PAI, SAI, and GIAI were performed by Kruskal-Wallis test, and comparisons between pre-COVID and COVID survey responses were made by paired t-test. For categorical variables, comparisons between 3 subtypes were made by the Chi-squared test, and between pre-COVID and COVID survey responses were made by McNemar's test. Factors associated with anxiety, stress, and difficulty with AI management were analyzed using logistic regression. P value < 0.05 was considered statistically significant.

Results

Participants

Of 342 patients who returned the COVID-19 supplemental survey, 157 (46%) had PAI, 109 (32%) had SAI, and 76 (22%) had GIAI. Median age at the time of survey completion was 61 (IQR: 46-69) years, 226 (65.9%) were women and 326 (95.0%) were Caucasians. At the time of survey, patients reported a median AI duration of 7 years (IQR: 4-14), longest in patients with PAI (median of 11 years vs 5 years in patients with SAI and GIAI, P = 0.0001) (Table 1).

COVID-19 Testing and Infections

Overall, 151 (44%) patients had at least 1 nasopharyngeal swab test for the SARS-CoV-2. Among them, 31 (21.4%) were tested in the setting of having symptoms suggestive of COVID-19 infection. More commonly, 84 (57.9%) were tested for mandatory reasons such as job requirement, medical procedures/hospitalizations for reasons other
| Parameter                                                                 | PAI (N = 157) | SAI (N = 109) | GIAI (N = 76) | Total (N = 342) | P       |
|---------------------------------------------------------------------------|---------------|---------------|---------------|----------------|---------|
| **Demographic information**                                               |               |               |               |                |         |
| Current age, years, median, IQR                                           | 60 (45-70)    | 61.5 (46-69.25) | 62.5 (49.25-69)| 61 (46-69)    | 0.7626  |
| Sex, female, (%)                                                          | 109 (69.4)    | 65 (59.1)     | 52 (68.4)     | 226 (65.9)    | 0.1870  |
| Race, Caucasian, (%)                                                      | 151 (96.2)    | 100 (90.9)    | 75 (98.7)     | 326 (95.0)    | 0.0376  |
| Duration of AI, years, median, IQR                                        | 11 (5-28)     | 5 (3-8)       | 5 (3-8)       | 7 (4-14)      | <0.0001 |
| **Financial impact and support system**                                   |               |               |               |                |         |
| Job affected (%)                                                          | 18 (20.5)     | 12 (25)       | 5 (27.8)      | 35 (22.7)     | 0.7184  |
| Financial loss > $5000 (%)                                                | 42 (33.3)     | 38 (42.2)     | 24 (38.1)     | 104 (37.3)    | 0.4071  |
| Moderate-to-high financial impact (%)                                     | 32 (21.2)     | 44 (41.9)     | 27 (35.5)     | 103 (31.0)    | 0.0013  |
| Difficulty with healthcare access (%)                                     | 33 (21.4)     | 39 (35.8)     | 31 (41.3)     | 103 (30.47)   | 0.0031  |
| Good medical insurance support (%)                                        | 129 (84.9)    | 87 (79.8)     | 59 (80.8)     | 275 (82.3)    | 0.5253  |
| Good family support (%)                                                   | 132 (85.2)    | 91 (84.3)     | 65 (85.5)     | 288 (85.0)    | 0.9678  |
| **Psychological impact and mental health (Depression, Anxiety and Stress Scale-21)** |               |               |               |                |         |
| Depression score, median, IQR                                             | 4 (0-10)      | 4 (2-15.5)    | 8 (2-14)      | 4 (2-12)      | 0.0317  |
| Depression score ≥10 (%)                                                  | 50 (32.1)     | 40 (37.0)     | 34 (45.3)     | 124 (45.3)    | 0.1447  |
| Depression moderate to severe                                              | 25 (16.0)     | 31 (28.7)     | 19 (25.3)     | 75 (22.1%)    | 0.0382  |
| Anxiety score, median, IQR                                                | 2 (0-6)       | 4 (0-10)      | 6 (2-12)      | 4 (0-8)       | 0.0005  |
| Anxiety score ≥8 (%)                                                      | 36 (22.9)     | 39 (36.1)     | 37 (49.3)     | 112 (32.9)    | 0.0002  |
| Anxiety moderate to severe                                                | 25 (15.9)     | 31 (28.7)     | 27 (36.0)     | 83 (24.4)     | 0.0017  |
| Stress score, median, IQR                                                 | 6 (0.5-13.5)  | 8 (0-20)      | 10 (4-16)     | 8 (2-15.5)    | 0.0553  |
| Stress score ≥15 (%)                                                      | 29 (18.6)     | 37 (33.9)     | 19 (25.3)     | 85 (25.0)     | 0.0176  |
| Stress moderate to severe                                                 | 16 (10.3)     | 30 (27.5)     | 15 (20.0)     | 61 (17.9)     | 0.0013  |
| **Self-management**                                                        |               |               |               |                |         |
| Daily hydrocortisone equivalent dose, milligram, median, IQR              | 20 (20-30)    | 20 (15-25)    | 20 (18-26.875)| 20 (17.625-25)| 0.0163  |
| Wearing medical alert gear (%)                                            | 136 (87.2)    | 83 (77.6)     | 58 (76.3)     | 277 (81.7)    | 0.0542  |
| Number of stress glucocorticoid used since COVID-19 started, median, IQR | 1 (0-3)       | 0 (0-2)       | 0 (0-2)       | 1 (0-3)       | 0.2850  |
| Use ≥ 1 dose of stress glucocorticoid since COVID-19 started (%)          | 87 (56.5)     | 53 (48.2)     | 36 (48.7)     | 176 (52.1)    | 0.3294  |
| Having injectable glucocorticoid at home (%)                              | 135 (86.5)    | 83 (76.15)    | 49 (64.5)     | 267 (78.3)    | 0.0005  |
| Use ≥ 1 injectable glucocorticoid since COVID-19 started (%)              | 12 (7.7)      | 13 (11.8)     | 7 (9.5)       | 32 (9.4)      | 0.5299  |
| Have ≥ 1 adrenal crisis since COVID-19 started (%)                        | 17 (10.9)     | 13 (11.8)     | 8 (10.7)      | 38 (11.1)     | 0.9621  |
| High self-perceived difficulty with AI management (%)                     | 42 (27.1)     | 40 (36.4)     | 32 (42.1)     | 114 (33.4)    | 0.0553  |
| **COVID-19 testing and infection**                                        |               |               |               |                |         |
| Number of COVID-19 test, median, IQR                                       | 0 (0-1)       | 0 (0-1)       | 1 (0-2)       | 0 (0-1)       | 0.0340  |
| Have ≥ COVID-19 test (%)                                                  | 63 (40.1)     | 46 (41.8)     | 42 (55.3)     | 151 (44.0)    | 0.0789  |
| Reasons for COVID-19 test                                                 |               |               |               |                |         |
| Asymptomatic but mandatory                                               | 29 (50.0)     | 29 (64.4)     | 26 (61.9)     | 84 (57.9)     | 0.5890  |
| Asymptomatic but for self-reassurance                                     | 15 (25.9)     | 8 (17.8)      | 7 (16.7)      | 30 (20.7)     | 0.9414  |
| Having symptoms suggestive of COVID-19 infection                           | 14 (24.1)     | 8 (17.8)      | 9 (21.4)      | 31 (21.4)     | 0.5222  |
| Positive COVID-19 infection                                               | 3 (4.8)       | 2 (4.4)       | 1 (4.0)       | 6 (4.0)       | —       |

Abbreviations: AI, adrenal insufficiency; COVID-19, coronavirus disease 2019; GIAI, glucocorticoid-induced adrenal insufficiency; IQR, interquartile range; PAI, primary adrenal insufficiency; SAI, secondary adrenal insufficiency.
than COVID-19, and travel. Another 30 (20.7%) patients were tested for self-reassurance because of history of AI or having exposure to known infected persons. Positive COVID-19 infection was confirmed in 6 patients. The positive rate in patients who were ever tested was 4.0%, and the overall prevalence COVID-19 infection was 1.8%. All patients reported mild symptoms, were managed conservatively at home, and were adherent to adrenal action plan by increasing dosage of glucocorticoids. None of the patients developed adrenal crisis or required parenteral glucocorticoids or hospitalization (Table 1).

Management of Adrenal Insufficiency During the Pandemic

Patients with AI reported taking chronic glucocorticoid therapy with hydrocortisone (260, 76.0%), prednisone (67, 19.6%), combination regimen (12, 3.5%), and dexamethasone (3, 0.9%). Patients with PAI reported the highest median HC equivalent daily replacement of 20 mg (IQR: 20-30) vs median of 20 mg (IQR: 15-25) in patients with SAI and median of 20 mg (IQR: 18-27) in patients with GIAI (P = 0.016) (Table 1). Most patients (277, 81.7%) were adherent with wearing medical alert gear, without differences among the 3 subtypes. However, patients with PAI reported higher rates of having injectable glucocorticoid available at home (PAI: 86.5% vs SAI: 76.2% vs GIAI: 64.5%, P = 0.0005). Since the pandemic started, the median usage of stress dose of glucocorticoid was 1 (IQR: 0-3), and 38 (11.1%) patients reported having adrenal crises that were unrelated to COVID-19 infections. Overall, 114 (33.4%) patients reported having difficulty with AI self-management during the pandemic, higher among patients with GIAI, followed by patients with SAI and PAI (42.1% vs 36.4% vs 27.1%, P = 0.055) (Table 1).

When compared to survey responses prior to the pandemic, daily glucocorticoid dose and the number of adrenal crises did not change. The number of stress dose of glucocorticoid usage within 1 year prior to survey completion was lower during the pandemic (median: 1 vs 3, P < 0.0001). Notably, the proportion of patients reporting having difficulty with AI self-management was significantly higher during the pandemic (32.9% vs 18.3%, P < 0.0001) [Table 2; Fig. 2A; also see Supplemental Table 2 in (19)].

Financial, Psychosocial, and Quality-of-Life Measures

Since the pandemic started, 22.7% of patients with AI reported losing jobs permanently or being furloughed. Monetary loss greater than $5,000 was reported in 37.7% patients, and 31.0% patients believed that the pandemic had caused moderate or high financial impact in their lives (Table 1). Furthermore, 30.5% patients experienced difficulties in attending medical visits or refilling relevant medications for AI, being higher in patients with GIAI than other subtypes (41.3% vs 35.8% in SAI vs 21.4% in PAI, P = 0.003). Good support from medical insurance company and family was reported in 82.3% and 85.0% of patients, respectively, and similar among 3 subtypes of AI (Table 1).

In total, 64.4% of respondents rated the psychological impact of the pandemic as moderate or severe: 22.1% reported moderate to severe depressive symptoms; 24.4% reported moderate to severe anxiety symptoms; and 17.9% reported moderate to severe stress levels (Table 1). The median depression score was 4 (IQR: 2-12) overall, being higher in patients with GIAI compared to SAI or PAI (median of 8 vs 4 in patients with PAI and SAI, P = 0.032). Similarly, patients with GIAI also had a higher anxiety score (median of 6 vs 4 in patients with SAI vs 2 in patients with PAI, P = 0.0005). The stress score was similar among 3 subtypes (median of 6 in patients with GIAI vs 4 in patients with SAI vs 2 in patients with PAI, P = 0.055) (Table 1).

Overall, the Z-scores in all 8 dimensions were less than 0, indicating that during the pandemic, patients with AI experienced a more impaired quality of life than the general population. The physical component summary score was 40.33 (SD: 12.66), highest in patients with PAI (43.46 ± 12.04) than patients with SAI (40.66 ± 12.32) and GIAI (33.39 ± 11.80, P < 0.0001), while the mental component summary score was 46.93 (SD: 11.74) and was similar among the 3 subtypes (P = 0.11) [Fig. 1; also see Supplemental Table 1 in (19)]. Overall, patients with PAI reported the highest quality of life while patients with GIAI reported the lowest scores in physical functioning, role-physical limitation, vitality, mental health, social functioning, body pain, and general health (all P < 0.05) [Fig. 1; also see Supplemental Table 1 in (19)].

When compared to survey responses prior to the pandemic, patients reported a higher financial impact from AI (33.9% vs 22.8%, P = 0.006) and difficulty accessing healthcare (6.7% vs 31.1%, P < 0.0001) during the pandemic. In contrast, more patients reported good family support since the pandemic started (84.0% vs 73.1%, P = 0.0012). In comparison to the pre-pandemic quality of life, patients reported higher scores in the physical component summary (mean: 39.6 vs 38.6, P = 0.04), and the 2 dimensions: role-physical limitation (mean of 52.63 vs 45.30, P = 0.0045) and vitality (mean of 42.12 vs 39.44, P = 0.009) during the pandemic. In contrast, the mental component summary score was similar pre- and during the pandemic (mean: 46.61 vs 46.97, P = 0.53), with a lower mental health dimension score during the pandemic (mean:
Factors Associated With a High Self-Perceived Difficulty With AI Management During the Pandemic

In the multivariate analyses, after adjusting for the duration and subtypes of AI, patients were more likely to report difficulty with managing AI if they were younger than 60 years (odds ratio (OR) 2.30, CI 95% 1.30-4.08), women (OR 3.69, CI 95% 1.92-7.09), had poor access to healthcare (OR 4.23, CI 95% 2.32-7.72), reported lack of good insurance support (OR 2.81, CI 95% 1.33-5.94), and experienced a higher financial impact (OR 2.32, CI 95% 1.26-4.27) [Fig. 3; also see Supplemental Table 3 in (19)].

Factors Associated With Anxiety and Stress During the Pandemic

Patients were more likely to report a higher anxiety score (≥8) if they found managing AI difficult during the pandemic (OR 3.83, CI 95% 1.69-8.65), higher difficulty managing AI (OR 3.70, CI 95% 1.50-9.09), and lower mental component summary score prior to the pandemic (OR 3.13, CI 95% 1.41-6.92) were associated with a higher stress score (≥15) [Fig. 4B; also see Supplemental Table 5 in (19)].

Discussion

In this study, we assessed self-reported quality of life, psychosocial metrics, and ability to self-manage AI during the COVID-19 pandemic. Notably, although patients’ AI therapy remained similar and no COVID-19 related adrenal crises occurred, one third of patients reported that AI management during the pandemic was difficult, and two thirds rated the negative psychological impact of the pandemic as moderate to severe. We identified a number of risk factors that were associated with self-perceived difficulties with AI management during the pandemic and a higher level of anxiety and stress.

In our cohort of patients with AI, 44% were tested for COVID-19, with a positive rate of 4.0% and an overall prevalence of COVID-19 infection of 1.8%. As a comparison, at the time of survey completion, the overall prevalence of COVID-19 infection in the United States was 7.9% and the positivity rate was 8.4% (2). Lower than national rate of COVID-19 infection was also reported by

Table 2. Comparison of self-management of adrenal insufficiency before and during the COVID-19 pandemic

| Parameter                                      | Before COVID-19                  | During COVID-19                  | P*     |
|------------------------------------------------|---------------------------------|---------------------------------|--------|
| Number of stress glucocorticoid used in the preceding year, median, IQR | 3 (1-6)                        | 1 (0-3)                         | <0.0001|
| Number of adrenal crisis in the preceding 1 year, mean, SD  | 0.17±0.36                      | 0.19±0.68                      | 0.6673 |
| Moderate-to-high financial impact (%)             | 54 (23.0)                      | 79 (33.6)                      | 0.0061 |
| Difficulty with healthcare access (%)         | 16 (6.7)                       | 74 (31.1)                      | <0.0001|
| High perceived difficulty with self-management (%) | 43 (18.1)                      | 78 (32.8)                      | <0.0001|
| Good family support (%)                        | 173 (72.7)                     | 200 (84.0)                     | 0.0012 |
| Good medical insurance support (%)             | 193 (83.6)                     | 189 (81.8)                     | 0.5050 |
| Quality of life (Short Form-36)                 |                                 |                                 |        |
| Physical Functioning, mean, SD                 | 66.08±28.69                    | 67.01±29.70                    | 0.4504 |
| Role-Physical Limitation, mean, SD             | 45.30±43.61                    | 52.82±43.43                    | 0.0045 |
| Body Pain, mean, SD                            | 61.34±27.95                    | 60.17±27.08                    | 0.3623 |
| General Health, mean, SD                       | 46.36±25.69                    | 46.43±25.38                    | 0.9458 |
| Social Functioning, mean, SD                   | 65.54±30.58                    | 65.13±30.24                    | 0.7885 |
| Role-Emotional Limitation, mean, SD            | 67.71±42.09                    | 69.57±39.83                    | 0.5010 |
| Vitality, mean, SD                             | 39.52±24.86                    | 42.12±24.90                    | 0.0090 |
| Mental Health, mean, SD                        | 72.57±19.29                    | 70.66±21.16                    | 0.0473 |
| Physical Component Summary, mean, SD           | 38.59±12.73                    | 39.57±12.38                    | 0.0423 |
| Mental Component Summary, mean, SD             | 46.97±11.92                    | 46.61±12.18                    | 0.5267 |

Abbreviations: COVID-19, coronavirus disease 2019; IQR, interquartile range; SD, standard deviation.

*Paired t-test for continuous variables and McNemar’s test for categorical variables.

70.66 vs 72.48, P = 0.047) [Table 2; Fig. 2A and 2B; also see Supplemental Table 2 in (19)].
Martino et al, where the prevalence of COVID-19 in patients with AI was 0.8%, as compared to 2.5% in Italy at the time of that study (17). Previous studies reported a higher susceptibility to infections and a higher likelihood to be hospitalized due to infections in both patients with PAI and SAI (5,6). Lower rates of COVID-19 infection in our patients with AI may be explained by a higher level of vigilance and better adherence to the state or nationwide social distancing and stay-at-home policies. Alternatively, there may be other dynamics related to testing frequency and symptomatic presentations in patients with AI that are not well understood or captured by our survey.

One notable strength of our study is that a substantial proportion of patients had completed a survey prior to the pandemic, thus permitting peripandemic comparisons. We found that in comparison to the prepandemic survey responses, patients with AI reported no changes in their daily glucocorticoid doses but a decreased usage of stress dosing during the pandemic. A higher number of patients reported better support from family and from the medical insurance during the pandemic, factors that we previously demonstrated to be important and associated with better outcomes in patients with AI (7). Patients also reported similar quality-of-life scores in most dimensions, notably with higher scores in the physical component summary, possibly as a result of reduced working hours, travel, or activities secondary to the lockdown measures during the pandemic. Notably, the number of patients reporting difficulties with AI management almost doubled since the pandemic started. We identified several factors associated with self-perceived challenges with AI management, with younger age, women, those with poor access to healthcare, lack of good insurance support, and those experiencing a higher financial impact of pandemic being important. The possible explanations for these findings could be pandemic-related increase in childcare responsibilities, lockdown measures, furlough, and loss in income, as well as possible difficulties with telemedicine access. Our findings are in line with several other studies that have reported younger patients and women were more vulnerable to the mental stress related to the pandemic (24,25), that easy access to telemedicine could achieve high patient’s satisfaction and meet their needs in other common endocrine conditions during the pandemic (26,27), and that good insurance coverage was associated with better self-perceived health in patients with AI (7).

In our study, we found that nearly two thirds of patients with AI rated the negative psychological impact during the pandemic as moderate to severe. Another study that also used the DASS-21 questionnaire in assessing psychological responses of a general population in China during the initial stage of the COVID-19 pandemic (from January to February 2020) reported a prevalence of 53.8% in the...
moderate to severe psychological impact (24). Differences in certain demographic factors such as ethnicity, cultural, or religious background could explain the differences in noted psychological resilience. However, it is more likely that the worsening COVID-19 spread in the United States in later 2020 and the superimposing AI among other comorbidities associated with AI contributed to a higher prevalence of depression, anxiety, or stress in our cohort.

Figure 2. (A) Comparison of socioeconomic factors before and during the COVID-19 pandemic. (B) Comparison of quality of life before and during the COVID-19 pandemic. Abbreviations: COVID-19, coronavirus disease 2019; SEM, standard error of the mean.
We identified that younger age, a lower quality of life prior to the pandemic, and reporting difficulties with AI management during the pandemic were associated with higher levels of anxiety and stress during the pandemic. Addressing the factors identified as important contributors to difficulties with AI management, such as access to healthcare during the pandemic, may alleviate the stress and anxiety experienced by patients with AI.

Given the large sample size of our study and inclusion of patients with GIAI in addition to patients with PAI and SAI, we were able to perform a subgroup analysis demonstrating several important differences in management based on AI subtypes. We found that patients with GIAI reported a substantially higher burden of disease during the pandemic. Patients with GIAI had a 2-fold higher depression score and anxiety score, reported a higher level of discomfort with AI management, and more impaired quality of life. In contrast, patients with PAI, despite having a longer duration of disease and taking a higher maintenance dose of glucocorticoids, reported better mental health and quality of life, although their quality of life was still more impaired as compared to sex- and decade-matched general population (22). In a smaller study of 121 patients with AI, Martino et al did not demonstrate any differences in the level of psychophysical stress and quality of life between patients with PAI and SAI during the pandemic (17). However, the absence of difference could also be attributed to a small sample size and lack of power. In addition to using a different questionnaire, geographic, and societal support differences, distinguishing patients with GIAI from other types of SAI was not possible in this smaller study. The differences observed in patients based on AI subtype in our study could have several explanations. In comparison to patients with SAI and GIAI, patients with PAI had a longer duration of disease, reported a higher compliance with wearing medical alert gear, higher availability of injectable glucocorticoids, a higher comfort level managing AI, and a better support system. In addition, patients with SAI likely had additional pituitary deficiencies that may have contributed to the differences in the quality of life during the pandemic. It is possible that patients with GIAI did not receive similar level of education for AI due to the anticipated temporary nature of AI by the treating physicians or patients themselves. In addition, many patients with GIAI were treated with glucocorticoids for an underlying inflammatory condition that may independently contribute to lower quality of life, depression, and anxiety (4).

Our study has several strengths, including a large sample size; a dual-center design; inclusion of patients with PAI, SAI, and GIAI; and the opportunity to compare the results to the prepandemic data. This is the first longitudinal survey
study of patients with AI in the United States providing unique insights into the care and management of AI within a different health system. We acknowledge several potential limitations, including selection, referral, nonrespondent, and recall biases. Patients included in the study were not only more likely to have been evaluated by an adrenal specialist, possibly had a higher socioeconomic status, and better access to healthcare but also had a higher likelihood of a more complicated course of AI at the time of initial evaluation. Therefore, the results may not be applicable to populations outside our tertiary care networks or non-US or non-Caucasian populations (as 95% of our study participants were Caucasian). Nonresponse bias is also common in survey research. The overall survey response rate was 48.5%. Based on the work of Beebe et al, using a mixed-mode, mail and telephone method, an overall response rate of 49% would be expected for medical survey research (28). The pre-COVID survey did not foresee the pandemic and therefore did not include psychological measures to allow a direct comparison in this regard. Recall bias was also likely for survey questions relating to symptoms during the COVID-19 infections and circumstances when stress glucocorticoids were used. In addition, the normative data of SF-36 were obtained prior to the COVID-19 pandemic and such population-based results are lacking during the pandemic. Therefore, the adjusted Z-scores based on it could overestimate the impairment in quality of life between patients with AI and their sex- and decade-matched general population. Given the low rate of COVID-19 infection, we were not able to conclude on comparative severity of COVID-19 infection in our cohort of patients. Negative/null observations may have been limited by sample size. Lastly, our definition of adrenal crisis depended on individual patient’s understanding and may not be identical to what professional guidelines referred to.

Conclusions

In conclusion, two thirds of the patients rated the psychological impact of the pandemic as moderate to severe. One third of patients with AI reported difficulties in AI management during the pandemic; the most vulnerable groups of patients with AI were younger individuals, women, and those with poor access to healthcare, with less support from medical insurance, and with higher financial burden. Difficulties with AI self-management in turn were associated with higher anxiety and stress. Patients with AI reported an impaired quality of life, which was more profound in those with GIAI or SAI. Our study calls for a more robust education, easily accessible healthcare, and societal support for all patients with AI, but especially for younger patients, women, and those with poor access to healthcare or financial resources.

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Data Availability: Some or all data sets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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