Gaps in the management of adrenal insufficiency in melanoma survivors: a retrospective cohort study

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Summary

Background Due to limited data on managing immunotherapy-induced secondary adrenal insufficiency (SAI) in melanoma survivors, this study investigated its management strategies and outcomes.

Methods This retrospective cohort study analyzed melanoma patients treated with immune checkpoint inhibitors (ICIs) with SAI (Mel_SAI, n = 161), without SAI (Mel_CON, n = 168), and patients with pituitary adenoma-related SAI (Pit_SAI, n = 106) at our institution from January 2013 to November 2023. We compared glucocorticoid management patterns, quality of life using distress scores, and the impact of different glucocorticoid types on survival outcomes using Kaplan–Meier analysis.

Findings Mel_SAI received significantly higher initial (median: 30 mg; IQR: 20–30 mg) and maintenance (median: 25 mg; IQR: 20–30 mg) hydrocortisone doses than Pit_SAI (initial: 20 mg; IQR: 15–30 mg; maintenance: 15 mg; IQR: 15–23 mg). Over half of Mel_SAI received prednisone as initial glucocorticoid replacement (n = 89, 55%), compared to 27% (n = 29) of Pit_SAI. Distress scores were significantly higher in Mel_SAI (median: 3; IQR: 2–5) than in Pit_SAI (median: 2; IQR: 1–3), but similar between Mel_CON. Prednisone use was associated with decreased survival in Mel_SAI (hazard ratio: 2.31; 95% CI: 1.14–4.46).

Interpretation Higher glucocorticoid doses and prednisone use in melanoma patients with SAI may be due to higher distress scores rather than SAI itself. Given the negative impact on survival and potential side effects, we recommend hydrocortisone at standard doses as the preferred glucocorticoid replacement in melanoma patients with SAI.

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Keywords: Secondary adrenal insufficiency; Cancer immunotherapy; Glucocorticoid replacement; Melanoma; Patient distress

Introduction

Immune checkpoint inhibitors (ICIs), targeting Cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), programmed cell death protein 1 (PD-1), and programmed death ligand-1 (PD-L1), have markedly improved survival rates in patients with metastatic melanoma.[1] Recent long-term data from Checkmate 067 demonstrate that the combination of nivolumab and ipilimumab results in a median overall survival of 71.9 months, compared to 19.9 months with ipilimumab monotherapy.[2] However, the increased use of ICIs is often associated with a rise in immune-related adverse events (irAEs), which may necessitate immunosuppressive treatments.[2] While irAEs are commonly linked to positive treatment responses, the potential negative effects of prolonged immune suppression on patient outcomes require careful consideration.

Secondary adrenal insufficiency (SAI) characterized by a deficient production of glucocorticoids due to ICI-induced hypophysitis or suppression of the

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Research in context

Evidence before this study

We conducted a literature search in PubMed and EMBASE from database inception to November 2023, using search terms including "immune checkpoint inhibitors", "adrenal insufficiency", "glucocorticoid replacement", and "melanoma". While immune checkpoint inhibitors have revolutionized melanoma treatment, they can cause secondary adrenal insufficiency (SAI) requiring long-term glucocorticoid replacement. Guidelines for managing pituitary adenoma-related SAI are well-established, recommending hydrocortisone at physiological doses. However, our search revealed no systematic studies or guidelines specifically addressing glucocorticoid management strategies in cancer patients with immunotherapy-induced SAI. Existing research primarily focused on SAI incidence and diagnosis, leaving a critical knowledge gap regarding optimal glucocorticoid choice and dosing in this unique population.

Added value of this study

Our study provides the first systematic comparison of glucocorticoid management patterns between melanoma patients with immunotherapy-induced SAI and those with pituitary adenoma-related SAI. We found that melanoma patients received significantly higher hydrocortisone doses and were more frequently prescribed prednisone compared to pituitary adenoma patients. Most importantly, we discovered that prednisone use was associated with decreased survival in melanoma patients with SAI, despite similar distress scores between melanoma patients with and without SAI. These findings challenge current prescribing practices and provide evidence-based guidance for glucocorticoid selection in this population.

Implications of all the available evidence

Our findings, combined with established endocrine guidelines, strongly suggest that standard-dose hydrocortisone should be the preferred glucocorticoid replacement therapy for melanoma patients with immunotherapy-induced SAI. The association between prednisone use and decreased survival emphasizes the need for careful glucocorticoid selection. Early endocrinologist involvement and adherence to endocrine guidelines are essential for optimal outcomes. Future prospective studies are needed to develop standardized guidelines specifically for managing immunotherapy-induced SAI in cancer patients.

hypothalamus-pituitary-adrenal axis (HPA) after chronic high-dose glucocorticoid treatment occur in a significant number of melanoma patients treated with ICIs.[3,4] SAI has significant impact on patients, causing psychological morbidity and reduced quality of life (QoL), and can be life-threatening if not properly treated.[5] To the best of our knowledge, no literature exists on assessing glucocorticoid replacement, QoL and distress, survival outcomes in melanoma patients with SAI.

This study aimed to investigate the management and outcomes of SAI in melanoma patients. Our objectives were to: (1) compare the type and dose of glucocorticoid between melanoma patients with SAI and patients with pituitary adenoma-related SAI; (2) compare QoL and distress scores between melanoma patients with SAI and patients with pituitary adenoma-related SAI, and between melanoma patients with/without SAI. In addition, we evaluated the impact of different glucocorticoid replacement therapies on overall survival in melanoma patients with SAI using Kaplan–Meier analysis. By addressing these aspects, we seek to fill the current knowledge gap in managing immunotherapy-induced SAI and its effects on QoL, distress, and survival outcomes in melanoma patients.

Methods

Study design

The primary goal of this study was to assess the needs and gaps in the management of SAI in advanced melanoma patients treated with cancer immunotherapy. To achieve this goal, we designed a multi-faceted approach. We compared the glucocorticoid type and dose, and distress scores between melanoma patients with SAI and patients with pituitary adenoma-related SAI. To assess the impact of cancer on QoL in melanoma patients, we compared distress scores between melanoma patients with and without SAI. Additionally, we evaluated the impact of glucocorticoid type on survival outcomes in melanoma patients.

Patients

The melanoma patients treated with cancer immunotherapy with/without SAI and patients with pituitary adenoma-related SAI were identified by utilizing the Research Patient Data Registry (RPDR) at our institution from January 2013 to November 2023. The RPDR, serving as a centralized clinical data repository, integrates information from various sources, including the Mass General Brigham Clinical Data Repository and the Epic systems at Brigham and Women's Hospital and Massachusetts General Hospital, among other affiliated hospitals.

Ethics

This study was approved by the Institutional Review Board of Mass General Brigham (Protocol Number: [2023P001615]). The requirement for informed consent was waived due to the retrospective nature of the study.

Groups

There were 3 groups in this study: Group 1. Melanoma patients with SAI (Mel_SAI). Group 2. Melanoma patients without SAI as melanoma control group (Mel_CON). Group 3. Patients with pituitary adenoma-related SAI (Pit_SAI). Patients in Mel_SAI group were identified using RPDR by searching relevant keywords in progress notes, specific ICD-10 codes, and medications including glucocorticoids and immune checkpoint inhibitors. The Mel_CON group was generated in two steps. First, an RPDR search identified 1522 melanoma patients who underwent ICI treatment without SAI. Second, we conducted matching in a 1:1 ratio with the Mel_SAI group, using age, sex, race, and comparative health as matching variables. The matching was performed using the match control function integrated within the RPDR. The Match Control query drawn patients from the selected RPDR population of patients (1522 melanoma patients who underwent ICI treatment without SAI). The patient match was a randomized match on patients across the selected patient population with a ranked order of matching. The order of ranked matching was gender, age, race, and comparative health. Age matching: Based on a patients age, the match control process filed patients into a particular age bin based on a span of 10 years. Gender Matching: Based on a patient's gender determined by the EHR sex code, patients were determined to be male, female or unknown/other and are identified as such within the match control process. Race Matching: Based on patient's demographic race code within the EHR, patients were categorized into 4 bins. The first grouping was for race code of 'White', the second grouping was for race code of 'Black', the third group was for a race code of 'Asian' and the fourth grouping was for all other race codes that do not meet the previous three. Comparative Health Match: Patients were matched based on categories of interaction within the health system. Similarly, the Pit_SAI group was generated by identifying 1036 patients through an RPDR search, followed by 1:1 matching to the Mel_SAI group using the same matching criteria. Following matching and initial data extraction, a comprehensive review of medical records was conducted to confirm the accuracy of diagnoses and treatment details.

Participant selection is shown in Fig. 1. From an initial pool of 690 subjects, equally distributed across the Mel_SAI, Mel_CON, and Pit_SAI groups (230 subjects per group), a total of 255 subjects were excluded for reasons including lack of confirmed secondary adrenal insufficiency, use of glucocorticoids for other diseases, immunotherapy for other malignancies, and missing medical records. Consequently, 435 subjects were included in the study, comprising 161 Mel_SAI patients, 168 Mel_CON patients, and 106 Pit_SAI patients. All included subjects have complete data on the primary variables of interest: endocrine clinic visits, distress scores, and glucocorticoid replacement types, with no additional missing values within these key variables.

Definition of SAI and glucocorticoid dose

SAI was defined as low or inappropriately normal ACTH with morning fasting cortisol level below 5 mg/dl or impaired cortisol response to ACTH-stimulation tests.[6] The maintenance replacement dose of glucocorticoid is defined as a daily dosage not exceeding 30 mg of hydrocortisone or its equivalent.[7] High dose glucocorticoid (HDG) was defied as glucocorticoid administration exceeding 10 mg of prednisone (or its equivalent) daily for a duration longer than one week. Adrenal crisis is defined as an acute deterioration in health evidenced by significant hypotension (either a systolic blood pressure below 100 mmHg or a reduction of $\geq$20 mmHg from the patient's usual level) that rapidly improves. Specifically, this involves a significant normalization of blood pressure within 1 h and an improvement in clinical symptoms within 2 h following the administration of parenteral stress dose of glucocorticoid.[8] Sick day education is defined as documented education during their clinic visit.

Quality of life and distress score

QoL was assessed using self-reported symptoms and the diagnosis of depression and/or anxiety. The self-reported symptoms included fatigue, pain, loss of appetite, low energy, muscle weakness, and insomnia. The distress score was calculated as the sum of all distress factors, with each self-reported symptom, depression, and anxiety counting as one point. It is important to note that this distress score has not been formally validated in prior research.

Statistical analysis

Statistical analyses for this study were performed using R software (version 3.6.4, R Foundation for Statistical Computing, Vienna, Austria). Descriptive statistics for continuous variables are presented as medians and interquartile ranges (IQRs). For categorical variables, appropriate statistical tests were applied based on the structure of the contingency tables. The chi-squared test with Yates' continuity correction was used for 2 × 2 contingency tables. When expected values were small, Fisher's exact test was used, with two-tailed p-values calculated as twice the one-tailed probability. For larger tables, such as 3 × 2 tables with small, expected counts, the Fisher-Freeman-Halton test was employed. Continuous variables between two groups were compared using the Mann–Whitney U test. A p-value of less than 0.05 was considered statistically significant.

Survival analysis was conducted for melanoma patients with AI who received ICI therapy. Overall survival (OS) was defined as the time from ICI therapy initiation to either death or censoring on February 14, 2024, for patients alive at analysis. The Kaplan–Meier method was

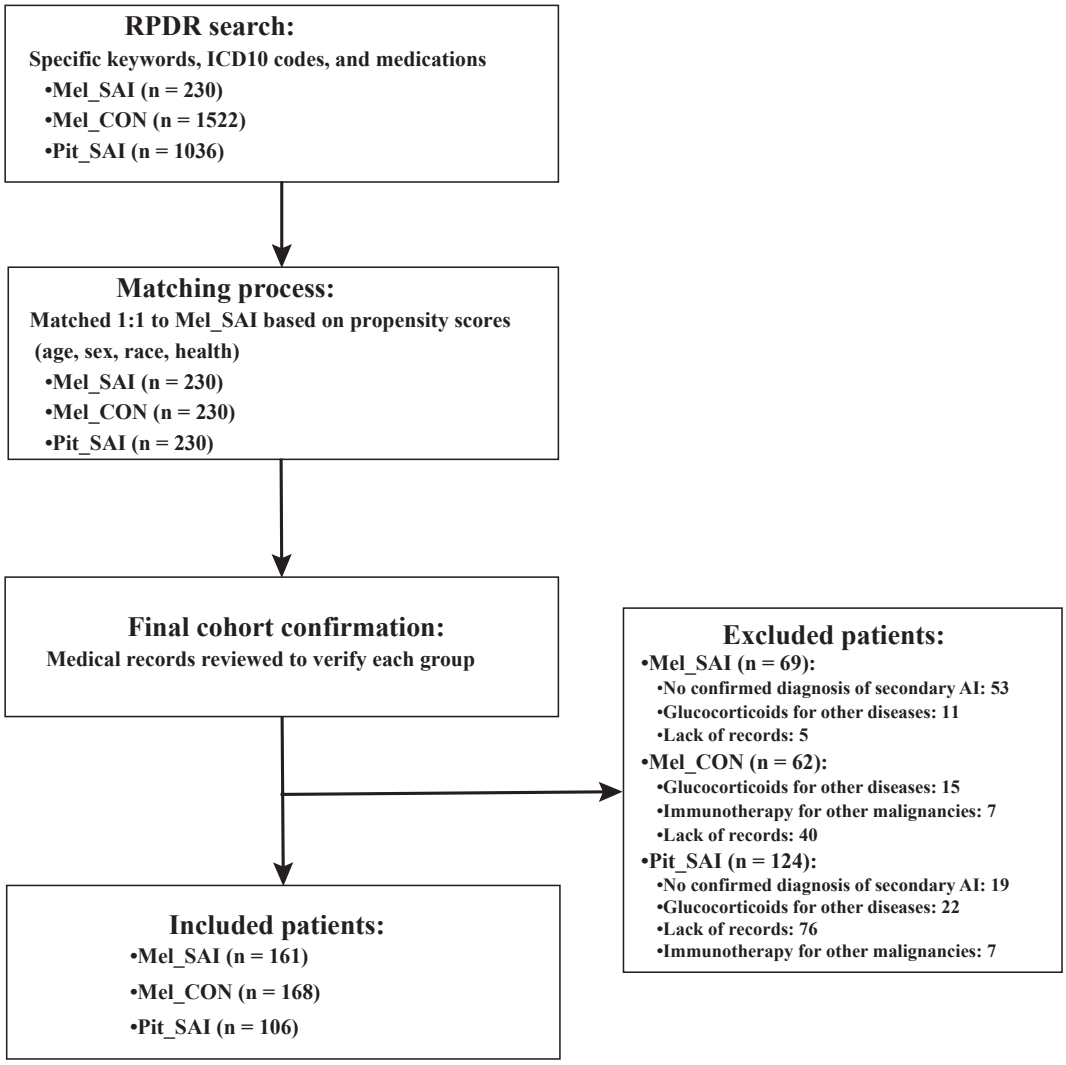

Fig. 1: **CONSORT flow diagram.** This flow chart illustrates the selection process of study participants. Out of an initial pool of 690 subjects (230 each in the Mel_SAI, Mel_CON, and Pit_SAI groups), 255 subjects were excluded due to lack of confirmed secondary adrenal insufficiency, use of glucocorticoids for other conditions, immunotherapy for other malignancies, and missing medical records. Consequently, 435 subjects were included in the study, all of whom have complete data on the key variables: endocrine clinic visits, distress scores, and glucocorticoid replacement types.

used to estimate OS probabilities, and the log-rank test was employed to compare OS between groups. Median survival times from Kaplan–Meier curves are reported with their corresponding 95% confidence intervals (CI).

Role of funding source

This study received no external funding. The authors had sole responsibility for study design, data collection, data analysis, data interpretation, and writing of the report.

Results

We compared the glucocorticoid replacement type and dose between the Mel_SAI (n = 161) and Pit_SAI (n = 168) groups (Table 1). A significantly higher proportion of patients in the Pit_SAI group (73%, n = 77) received hydrocortisone as the initial glucocorticoid replacement, whereas more patients in the Mel_SAI group (55%, n = 89) received prednisone as initiating replacement glucocorticoid ($p < 0.0001$). The median (IQR) initiating dose of hydrocortisone and prednisone were 30 (20, 30) mg and 5 (5, 10) mg in Mel_SAI, and 20 (15, 30) mg and 5 (4, 5) mg in Pit_SAI respectively ($p < 0.0001$ for hydrocortisone; $p < 0.0001$ for prednisone). The initial replacement doses of hydrocortisone and prednisone were significantly higher in the Mel_SAI group than in the Pit_SAI group ($p < 0.0001$, Table 1). The median (IQR) maintenance doses were 25

Characteristic	Mel_SAI N = 161	Pit_SAI N = 106	p-value
Age (Median (IQR)) **(years)**	66 (59, 77)	65 (54, 75)	0.12
Gender: Male/Female (n (%))	109 (68)/52 (32)	56 (53)/50 (47)	**0.020**
Initial GC replacement			
HC/Pred (n (%))	72 (45)/89 (55)	77 (73)/29 (27)	**<0.0001**
HC (Median (IQR)) (mg)	30 (20, 30)	20 (15, 30)	**<0.0001**
Pred (Median (IQR)) (mg)	5.0 (5.0, 10.0)	5.0 (4.0, 5.0)	**<0.0001**
Maintenance GC replacement			
HC/Pred/Dex (n (%))	75 (47)/81 (50)/5 (3)	80 (75)/25 (24)/1 (1)	**<0.0001**
HC (Median (IQR)) (mg)	25 (20, 30)	15 (15, 23)	**<0.0001**
Pred (Median (IQR)) (mg)	5.0 (4.0, 7.5)	5.0 (4.0, 5.0)	0.73
Sick day education (n (%))	151 (94)	103 (97)	0.33
Adrenal crisis (n (%))	27 (17)	28 (26)	0.080
HDG (n (%))	125 (78)	10 (9)	**<0.0001**
Hypothyroidism: No/Primary/Secondary (n (%))	52 (32)/57 (35)/52 (32)	13 (12)/2 (2)/91 (86)	**<0.0001**
Hyponatremia (n (%))	128 (80)	73 (69)	0.068
Hypoglycemia (n (%))	57 (35)	45 (42)	0.30

Mel_SAI: melanoma with secondary adrenal insufficiency; Pit_SAI: pituitary adenoma patients with secondary adrenal insufficiency; GC: glucocorticoid; HC: hydrocortisone; Pred: prednisone; Dex: dexamethasone; HDG: high dose glucocorticoid. A p-value of less than 0.05 was considered statistically significant indicated in bold.

Table 1: **Comparative analysis of demographic and clinical characteristics between Mel_SAI and Pit_SAI groups.**

(20, 30) mg and 15 (15, 23) mg for hydrocortisone, and 5 (4, 7.5) mg and 5 (4, 5) mg for prednisone, in the Mel_SAI and Pit_SAI groups, respectively. The maintenance hydrocortisone dose was significantly higher in the Mel_SAI group ($p < 0.0001$), while there was no statistically significant difference in the maintenance prednisone dose between the two groups ($p = 0.73$). In line with the initial replacement glucocorticoid type, a significantly higher proportion of patients in the Pit_SAI group (75%, n = 80) received hydrocortisone as maintenance replacement compared to those in the Mel_SAI group (47%, n = 75) ($p < 0.0001$). Additionally, 3% (n = 5) of patients in the Mel_SAI group received dexamethasone as glucocorticoid replacement, compared to 1% (n = 1) in the Pit_SAI group. A significantly higher proportion of Mel_SAI patients (78%, n = 125) received high-dose glucocorticoid treatment compared to the Pit_SAI group (9%, n = 10) ($p < 0.0001$).

The incidence of secondary hypothyroidism was significantly higher in the Pit_SAI group (86%, n = 91) than in the Mel_SAI group (32%, n = 52) ($p < 0.0001$). Hyponatremia was more common in the Mel_SAI group (80%, n = 128) than in the Pit_SAI group (69%, n = 73), although this difference was not statistically significant ($p = 0.07$). Similarly, adrenal crisis occurred in 17% (n = 27) of patients in the Mel_SAI group and 26% (n = 28) of patients in the Pit_SAI group, with no statistically significant difference ($p = 0.08$). Additionally, there were no statistically significant differences between the groups in the incidence of hypoglycemia ($p = 0.30$) or the administration of sick day education ($p = 0.33$) (Table 1).

We compared the number of endocrine clinic visits within the first 5 years after the diagnosis of SAI between Mel_SAI (n = 64) and Pit_SAI (n = 86) patients who survived for at least 5 years. The median number of clinic visits within 5 years was significantly higher in Pit_SAI (7, IQR: 4–9 visits) compared to Mel_SAI (4, IQR: 2–6 visits) ($p < 0.0001$) (Fig. 2). This analysis included only patients who survived for 5 years or more after the diagnosis of SAI.

We compared the distress scores between the Mel_SAI (n = 161) and Pit_SAI (n = 106) groups. The incidence of anxiety, fatigue, pain, low energy, weakness, insomnia, and alcohol use was significantly higher in the Mel_SAI group compared to the Pit_SAI group (Supplementary Figure S1A). The median distress score was significantly higher in the Mel_SAI group (3, IQR: 2–5) than in the Pit_SAI group (2, IQR: 0–3) ($p < 0.0001$) (Fig. 3A). To explore the impact of melanoma on distress scores, we also compared the distress scores between the Mel_SAI (n = 161) and Mel_CON (n = 168) groups. There was no statistically significant difference in the overall distress scores between the Mel_SAI group (median: 3, IQR: 2–5) and the Mel_CON group (median: 3, IQR: 2–5) ($p = 0.54$) (Supplementary Figure S1B and Fig. 3B). Supplementary Table S2 represents a comparative analysis of demographic and clinical characteristics between Mel_SAI patients receiving different types of maintenance glucocorticoid replacement. Within the Mel_SAI group, we performed a subgroup analysis to compare the distress scores between patients receiving maintenance hydrocortisone replacement (n = 75) and those receiving maintenance prednisone (n = 81) (Supplementary Figure S1C and

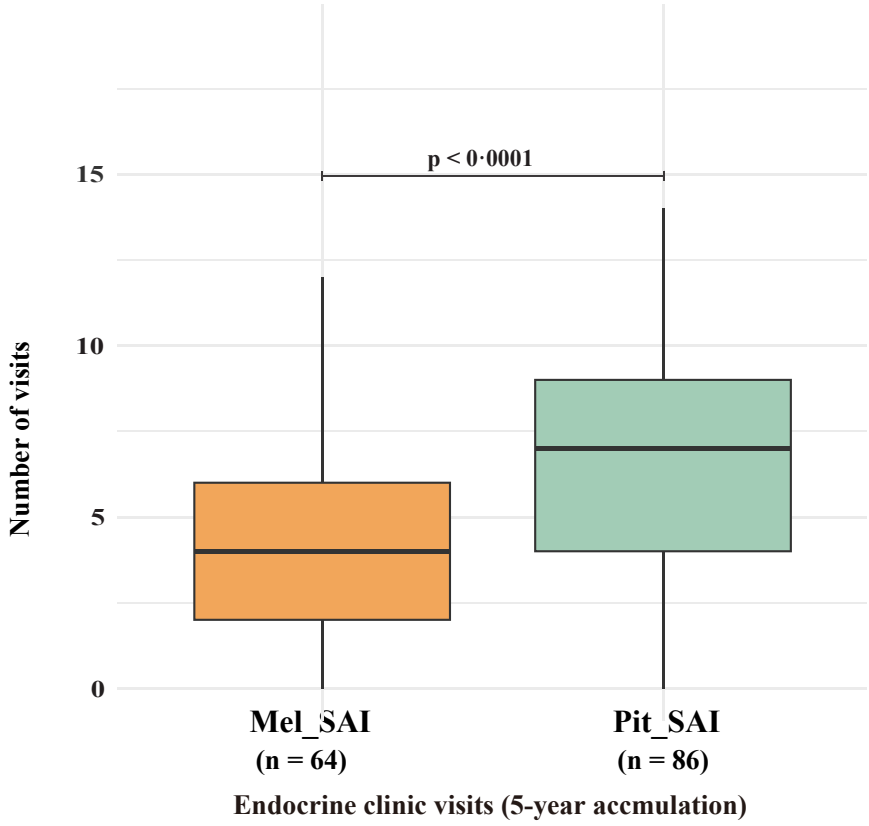

Fig. 2: **Cumulative 5-year endocrine clinic visits: Comparison between Mel_SAI and Pit_SAI groups**. This box plot compares the median number of endocrine clinic visits accumulated over 5 years between Mel_SAI (n = 64) and Pit_SAI (n = 86) groups. The box represents the interquartile range (IQR; 25th to 75th percentiles), the horizontal line within the box denotes the median, and the whiskers extend to the minimum and maximum values. Only patients who survived for 5 years or more were included in this analysis. **Statistical analysis**: Continuous variables between groups were compared using the Mann–Whitney U test. A p-value of less than 0.05 was considered statistically significant. **Abbreviations:** Mel_SAI: Melanoma patients with secondary adrenal insufficiency; Pit_SAI: Pituitary adenoma patients with secondary adrenal insufficiency.

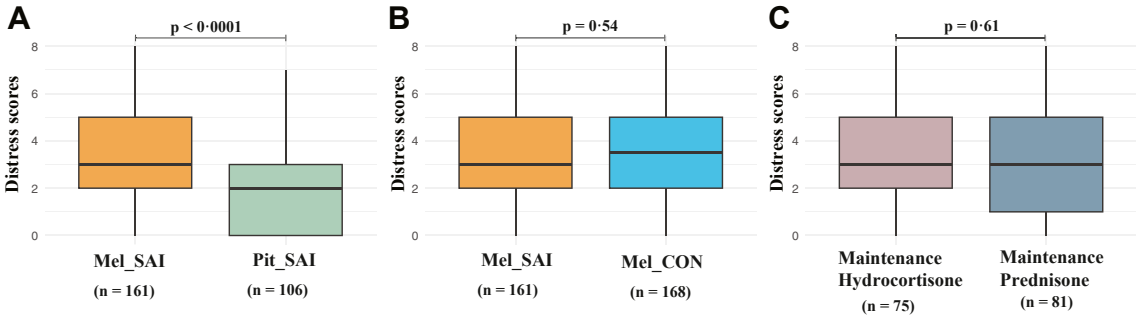

Fig. 3: **Comparison of distress scores among various patient groups**. A. Distress scores between Mel_SAI (n = 161) and Pit_SAI (n = 106) groups. B. Distress scores between Mel_SAI (n = 161) and Mel_CON (n = 168) groups. C. Distress scores between patients receiving maintenance hydrocortisone replacement (n = 75) or maintenance prednisone replacement (n = 81). The box plots display the median (horizontal line within the box), the interquartile range (IQR; boundaries of the box, representing the 25th and 75th percentiles), and the minimum and maximum values (whiskers). **Statistical analysis**: Continuous variables between groups were compared using the Mann–Whitney U test. A p-value of less than 0.05 was considered statistically significant. **Abbreviations:** Mel_SAI: melanoma patients with secondary adrenal insufficiency; Pit_SAI: pituitary adenoma patients with secondary adrenal insufficiency; Mel_CON: melanoma without secondary adrenal insufficiency.

Supplementary Table S2). There was no statistically significant difference in the distress scores between the maintenance hydrocortisone subgroup (median: 3, IQR: 2–5) and the maintenance prednisone subgroup (median: 3, IQR: 1–5) (p = 0.61) (Fig. 3C).

Survival analysis was performed to assess the impact of maintenance glucocorticoid type on OS in Mel_SAI patients in the first 5 years (Fig. 4). Within this period, mortality rates were 32% (12 deaths) for patients receiving maintenance hydrocortisone (n = 37) and 56% (23 deaths) for those receiving maintenance prednisone (n = 41). Kaplan–Meier analysis revealed decreased OS in patients receiving prednisone compared to hydrocortisone (log-rank p = 0.016, HR: 2.31, 95% CI: 1.14–4.46). The median survival time for patients receiving hydrocortisone was 55 months (95% CI: 47- Not Reached), while the median survival time for those receiving prednisone was 38 months (95% CI: 33- Not Reached).

Discussion

The primary objective of this study was to evaluate the management gaps and needs of cancer patients suffering from cancer immunotherapy-related SAI. We chose melanoma patients because melanoma is one of the malignancies commonly treated with cancer immunotherapy. Our evaluation focused on the type and dosage of glucocorticoid replacement therapy and distress score, comparing melanoma patients to individuals without malignancy but with pituitary adenoma-related SAI. We selected patients with pituitary adenoma-related SAI as a control group, given that pituitary adenoma is a prevalent cause of SAI. Additionally, to minimize confounding factors related to melanoma, we included a control subgroup of melanoma patients who underwent cancer immunotherapy but did not develop SAI.

In our study, we found differences in glucocorticoid type and replacement dose between Mel_SAI group and Pit_SAI group. In the Mel_SAI group, the initiation and maintenance doses of glucocorticoid were significantly higher than those in the Pit_SAI group. Additionally, more patients received prednisone as the initiating and maintaining glucocorticoid in the Mel_SAI group (Table 1).

Although the exact factors contributing to the differences in glucocorticoid dose and type between these

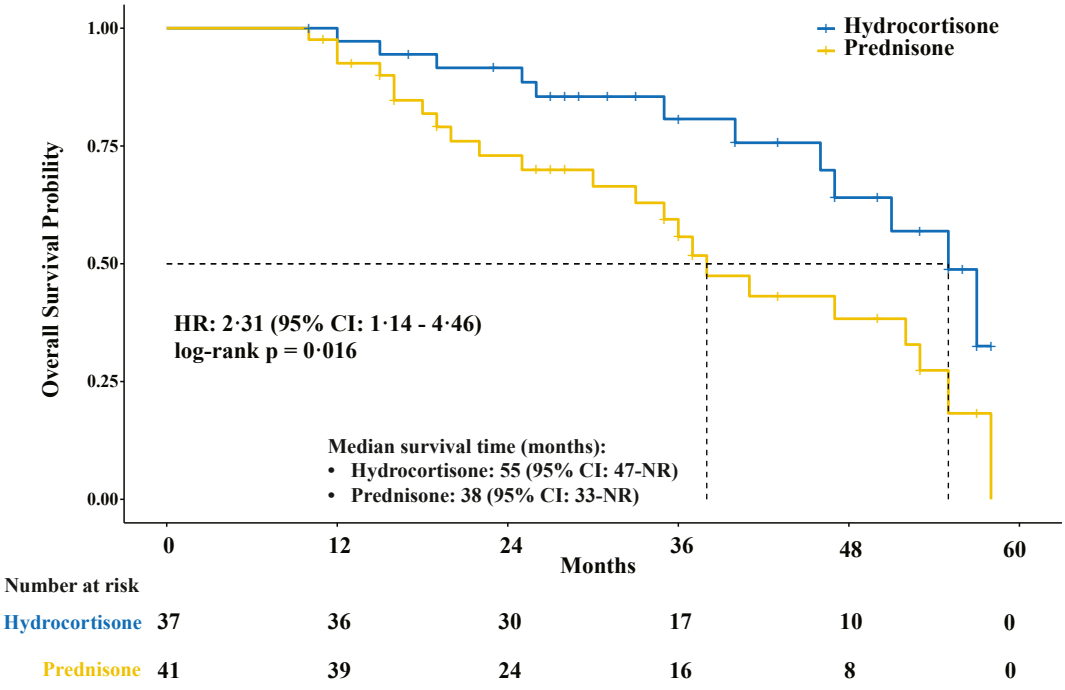

Fig. 4: **Impact of glucocorticoid replacement type on overall survival in Mel_SAI patients: Kaplan–Meier analysis**. Kaplan–Meier curves compare overall survival based on the type of the maintenance glucocorticoid replacement in Mel_SAI patients who survived less than 5 years. The hydrocortisone group (n = 37) is represented by the blue line, and the prednisone group (n = 41) is represented by the yellow line. The dashed line indicates the median survival time for each group. Results are presented as hazard ratios (HR) with 95% confidence intervals (CIs), and survival time is displayed in months. A table below the Kaplan–Meier curves shows the number of patients at risk at different time points (in months). The median survival time for patients receiving hydrocortisone was 55 months (95% CI: 47-NR), while the median survival time for those receiving prednisone was 38 months (95% CI: 33-NR). **Statistical analysis**: Survival analysis was performed using log-rank test and Cox proportional hazards model. A p-value of less than 0.05 was considered statistically significant. **Abbreviations**: Mel_SAI: melanoma with secondary adrenal insufficiency; HR: Hazard ratios; 95% CI: 95% confidence interval; NR: not reached.

two groups remain to be fully understood, several impacts could contribute to this gap. First, SAI in Pit_SAI patients was mainly managed by endocrinologists from the onset of SAI manifestation, as endocrinologists are typically involved in the management of most pituitary adenomas at or before the development of SAI. In contrast, the majority of SAI cases in Mel_SAI patients were managed by oncologists or primary care providers, especially at the early stage of SAI clinical manifestation, because these providers were usually the first to recognize and start the management of SAI in Mel_SAI patients. Our study showed fewer endocrine clinic visits in the Mel_SAI group compared to the Pit_SAI group. This finding supports the notion that differences in care by endocrinologists versus non-endocrinologists could contribute to the use of different types and doses of glucocorticoid in the management of SAI. It is therefore important to refer cancer patients to endocrinologists early when they develop SAI and to educate them on the importance of complying with endocrine clinic visits.

Second, differences in comorbidities and distress between Pit_SAI and Mel_SAI patients could also contribute to variations in the dose and type of glucocorticoid used in these two groups. Many patients in the Mel_SAI group also developed other immune-related adverse events (irAEs) requiring anti-inflammatory treatment with prednisone or dexamethasone.[9–11] Patients treated with ICIs who develop hypophysitis can experience severe and refractory headaches, which could lead to the necessity for high-dose glucocorticoid treatment.[12] In this study, we found that significantly higher percentage of patients in Mel_SAI received high dose glucocorticoids than in Pit_SAI. Eventually, these patients remained on prednisone or dexamethasone as replacement glucocorticoid for their SAI. Our study has shown that distress scores are significantly higher in Mel_SAI patients compared to Pit_SAI patients (Fig. 3A). The higher distress scores could lead to a higher replacement dose of glucocorticoid in cancer patients.

Previous studies have suggested that a higher dose of glucocorticoid replacement does not improve QoL outcomes in patients with SAI.[13,14] Current endocrine guidelines recommend a replacement dose of hydrocortisone between 15 and 25 mg daily in divided doses.[15] There is growing evidence suggesting that daily doses above 20 mg of hydrocortisone replacement could adversely affect patients' metabolism and mortality.[16–18] Some recent literature suggests using lower replacement glucocorticoid doses in SAI.[6,19] Given that our findings in this study show that the significantly higher distress scores in Mel_SAI patients were primarily related to melanoma rather than SAI (Fig. 3), it is likely that melanoma patients with SAI do not need a higher replacement glucocorticoid dose.

In our study, we have shown that in Mel_SAI patients, there is no statistically significant difference in distress scores between those on hydrocortisone or prednisone replacement (Fig. 3C). Additionally, prednisone replacement was associated with decreased OS (Fig. 4). Prednisone is commonly used as an anti-inflammatory agent in the management of irAEs. It is possible that the use of prednisone as replacement glucocorticoid in SAI may be associated with the presence of other coexisting irAEs. However, we did not investigate this association in the current study. In future research, it will be important to explore this potential link to determine whether it contributes to the increased use of prednisone as a replacement therapy in melanoma patients with SAI. Since hydrocortisone is recommended as the first-choice glucocorticoid in current endocrine guidelines,[15] We suggest using hydrocortisone as the routine glucocorticoid replacement for cancer patients with SAI whenever possible. The findings of our study indicate that patients with Mel_SAI had fewer endocrine clinic visits compared to those with Pit_SAI. This disparity may be attributed to a primary focus on managing melanoma, potentially at the expense of monitoring endocrine complications (Fig. 2). Therefore, it is important to educate patients on the necessity of adhering to their endocrine clinic visits.

Adrenal crisis can be life-threatening if not properly managed. In our study, we observed a lower incidence of adrenal crisis in melanoma patients with SAI, although this difference was not statistically significant. This finding could be related to multiple factors. First, education on adrenal sick day rules is a standard practice in our institutions; as shown in Table 1, over 90% of patients in both groups received such education. Proper adjustment of glucocorticoid doses during illness is crucial for reducing the risk of adrenal crisis. Second, diagnostic bias may contribute to the observed difference. The nonspecific symptoms of adrenal crisis can complicate accurate diagnosis, potentially leading to underreporting. Third, some patients who experienced an adrenal crisis may have presented to local hospitals, and their medical information was not available to us, resulting in incomplete data. These factors together might explain the non-statistical lower incidence of adrenal crisis in melanoma patients observed in our study.

This study has several limitations. Firstly, being a retrospective study, it inherently contains biases related to the selection and availability of data. Secondly, the specificity of our patient demographic further limits the generalizability of our findings, highlighting the need for studies across more diverse populations and different type of malignancies. Additionally, the use of an unvalidated distress score, although constructed based on clinically relevant symptoms and diagnoses, may affect the reliability and generalizability of our findings. Our reliance on existing medical records for QoL assessments could have compromised the accuracy of identifying influencing factors, potentially skewing our understanding of the effects of glucocorticoid

replacement therapy. Another limitation is the potential bias introduced by missing cases due to incomplete records, which may have affected the representativeness of the study population. Furthermore, treating the control and comparison groups as independent, despite a mix of paired and independent samples, may have reduced the efficiency of our analysis. While this approach was practical for the current study, future research should consider more advanced methods to address mixed sample types. While our analysis indicates that using prednisone as a replacement glucocorticoid for SAI is associated with shorter overall survival, the absence of disease-specific features and complete irAE data in the survival analysis may introduce bias. However, it is important to note that survival analysis was not the primary objective of this study. To address these limitations, future research should adopt a prospective design, allowing for a more definitive examination of the causal relationships between glucocorticoid replacement dosing, distress, and mortality, particularly through longitudinal studies.

Contributors

Conception and design: L. Min.

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Drafting of the article: W.Lin, L.Min., F. Stephen Hodi.

Critical revision of the article for important intellectual content: L.Min, W. Lin, W. Wang, and F. Stephen Hodi.

Provision of study materials or patients: L. Min.

Administrative, technical, or logistic support: L.Min.

Collection and assembly of data: W. Lin, L. Min.

Final approval of the article: All authors (W. Lin, L. Min, W. Wang, and F. Stephen Hodi).

The underlying data was verified by L. Min and W. Lin. All authors read and approved the final version of the manuscript.

Data sharing statement

Some or all datasets generated during and/or analyzed during the current study are not publicly available due to patient privacy restrictions and institutional policies but are available from the corresponding author on reasonable request. Study protocol: Available from Dr. Min (e-mail, lmin@bwh.harvard.edu). Statistical analysis was performed using R software (version 3.6.4); the analysis scripts and code are available from the corresponding author upon reasonable request. Data set: Not available.

Declaration of interests

Dr. F. Stephen Hodi reports grants from Bristol Myers Squibb, Melanoma Research Alliance, and National Institutes of Health; consulting fees from Bristol Myers Squibb, Merck, Novartis, Compass Therapeutics, Apricity, Bicara, Checkpoint Therapeutics, Genentech, Bioentre, Gossamer, Iovance, Catalym, Immunocore, Kairos, Theos, Bayer, Zumutor, Corner Therapeutics, Puretech, Curis, AstraZeneca, Pliant, Solu Therapeutics, Vir Biotechnology, and 92 Bio; support for attending meetings from George Washington University; leadership or fiduciary roles with Bicara and Apricity; and stock or stock options in Bicara, Apricity, Checkpoint Therapeutics, Corner Therapeutics, and Solu Therapeutics. Dr. F. Stephen Hodi also holds multiple patents related to cancer treatment and diagnostics (patent numbers and details available upon request). All other authors declare no competing interests.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2024.102984.

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