Exploring Inpatient Hospitalizations and Morbidity in Patients With Adrenal Insufficiency

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Context: Patients with adrenal insufficiency (AI) (primary AI [PAI], secondary AI due to a pituitary disorder [PIT] and congenital adrenal hyperplasia [CAH]) have reduced life expectancy; however, the underlying explanation remains unknown.

Objective: To evaluate characteristics, comorbidities, and hospitalizations in AI patients.

Design: Retrospective observational.

Setting and Population: Using a United States-based national payer database comprising of more than 108 million members, strict inclusion criteria including diagnostic codes and steroid prescription records were used to identify 10 383 adults with AI; 1014 with PAI, 8818 with PIT, and 551 with CAH. Patients were matched 1:1 to controls, based on age (±5 y), gender, insurance, and region and followed for more than 12 months.

Intervention: None.

Main Outcome Measures: Demographic variables, comorbidities (diabetes mellitus [DM] types 1 and 2, depression, anxiety, hyperlipidemia, hypertension) and hospitalization incidence.

Results: Compared with controls, patients with AI had higher odds of DM, hypertension, hyperlipidaemia, depression, and anxiety, ranging from an odds ratio (OR) of 1.51 for hyperlipidaemia in PAI to 3.85 for DM in CAH. Odds of having DM (OR, 3.85; 95% confidence interval, 2.52–5.90) or anxiety (OR, 2.99; 95% confidence interval, 2.02–4.42) compared with controls were highest in CAH, whereas depression was highest in PAI and PIT (OR, 2.40 and 2.55). ORs of hyperlipidaemia and hypertension (OR, 1.98 and 2.24) were highest in the PIT cohort. Inpatient admissions were more frequent in PAI (4.64:1; $P < .0001$) and PIT (4.00:1; $P < .0001$) than controls; infection was the most common cause for admission.

Conclusion: Patients with AI carry a significant metabolic and psychiatric burden, with higher risk of comorbidities and hospital admissions than matched controls. **(*J Clin Endocrinol Metab* 101: 4843–4850, 2016)**

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Abbreviations: AI, adrenal insufficiency; CAH, congenital adrenal hyperplasia; CI, confidence interval; DM, diabetes mellitus; HYDRO, hydrocortisone; ICD, International Classification of Diseases; OR, odds ratio; PAI, primary AI; PIT, secondary AI due to a pituitary disorder; US, United States.

Adrenal insufficiency (AI) can be classified as primary AI (PAI) when a disease affects the adrenal glands or secondary AI due to a pituitary disorder (PIT) disrupting adrenocortocotropin secretion producing solely glucocorticoid deficiency, because the renin-angiotensin-aldosterone system remains intact (1). Most PAI or Addison's disease in the developed world (80%–90%) is attributed to autoimmune adrenalitis, with tuberculosis being a common cause in developing countries (2, 3). Although precise measurements of disease prevalence are not known, PIT has an estimated prevalence of 2.82 per 10 000 (4–6). Estimates of PAI or Addison's disease have been variable, but our analysis of the reported datasets show an overall prevalence rate of 1.21 per 10 000; generally, rates are higher in Scandinavian countries (7–14). Congenital adrenal hyperplasia (CAH) is a specific inherited cause of PAI that affects 1/10 000 to 1/20 000 newborns (2).

When left untreated, most AI patients die within 2 years of diagnosis (15, 16), but with the discovery of cortisone in the late 1940s and then its active metabolite, cortisol, life-long steroid replacement therapy followed (2, 17) with the assumption that life expectancy would be normal (18–20). However, recent studies show a 2-fold increase in standardized mortality in PAI and PIT patients resulting in a reduced life expectancy of 3.2–11.2 years (5, 21–26). The increased mortality observed in PAI is largely due to cardiovascular diseases and infections (21, 25, 26). Underpinning morbidity studies to date have been constrained by the relative rarity of AI and have involved small European based cohorts that have variably reported reduced bone mineral density, hypertension, metabolic syndrome, abnormal glucose tolerance, and reduced quality of life (17). Increased hospital admission rates due to infections and high rate of adrenal crisis have also been reported in European cohorts of patients with AI (14, 26, 27).

This study used a large national payer database in the United States (US) with the aim of evaluating patient characteristics, prevalence of chronic metabolic and psychiatric comorbidities common to AI patients, and subsequent incidence of hospitalization within each AI cohort compared with a sample of the general population in the database.

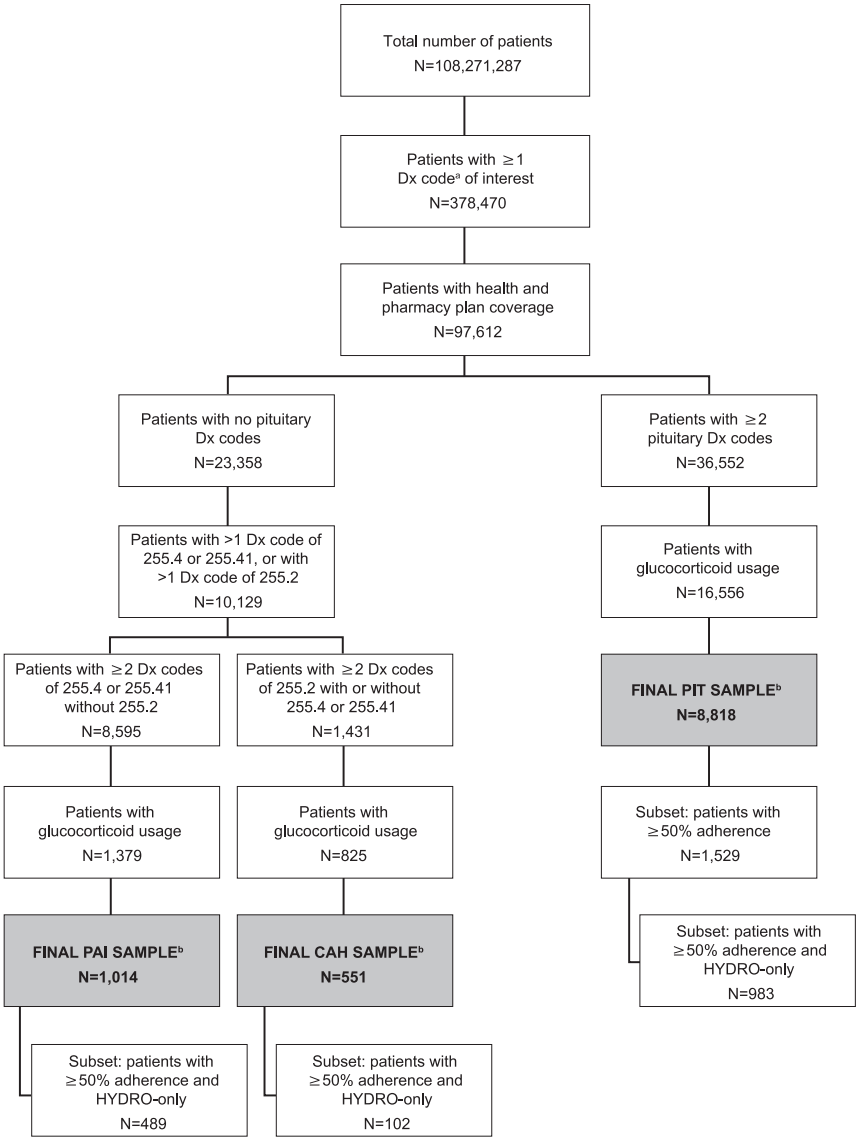

Figure 1. Attrition diagram. Dx codes of interest are listed in Supplemental Table 1. Final AI samples matched to a general population cohort by age, gender, insurance type and region. Dx, Diagnosis based on ICD-9, codes.

Materials and Methods

Data source

This study used administrative health claims data from Truven Health MarketScan Commercial and Medicare databases from January 2006 to June 2011, including a total of 108 271 287 patients. MarketScan contains individual-level, deidentified, healthcare claims information from employers, health plans, hospitals, Medicare, and Medicaid programs in the US. Having appropriate measures of patient deidentification in compliance with the US Health Insurance Portability and Accountability Act legislation, the MarketScan databases from Truven Health are the gold standard in proprietary databases used for US healthcare research. They are the ba-

sis of over 700 peer-reviewed articles published in leading journals since the first article by Hillman et al appeared in 1990 (28, 29).

Cohort definitions and selection criteria

Patients were classified into 3 cohorts (PAI, PIT, or CAH) based on their International Classification of Diseases (ICD)-9 diagnosis codes and pharmacy prescription fill orders (Figure 1). PAI was defined as any patient with at least 2 separate claims on different days of corticoadrenal insufficiency (255.4) or glucocorticoid deficiency (255.41), without a diagnosis of adrenogenital disorder (255.2) or any of the diagnoses associated with the PIT cohort (see Supplemental Table 1 for the list of ICD-9 codes, ICD-10 was not adopted in the US until October 2015). In addition, patients classified in the PAI cohort were required to have evidence of both glucocorticoid (prednisone, dexamethasone, or hydrocortisone [HYDRO]) and mineralocorticoid (fludrocortisone) usage. Secondary AI (PIT) was defined as any patient with at least 2 separate claims on different days of pituitary disease (Supplemental Table 1) and documented glucocorticoid usage. Lastly, CAH was defined as any patient with at least 2 separate claims on different days with the diagnosis code of 255.2 without any of the diagnoses associated with the PIT cohort and documented glucocorticoid usage. Once patient cohorts were defined, the following inclusion criteria were applied: patients had to have continuous health and pharmacy coverage starting at least 6 months before and for at least 12 months after first diagnosis on record (time 0). In order to exclude patients who may have been prescribed high doses of steroids for conditions other than AI, in all cohorts, patients were excluded if there was documentation of glucocorticoid and/or mineralocorticoid usage with a pharmacy fill within the last 30 days of prednisolone/prednisone more than 10 mg, dexamethasone more than 1 mg, or HYDRO more than 50 mg/d.

For the PIT cohort, a subset was constructed for patients with more than or equal to 50% adherence. This is a claims database and therefore adherence can only be measured based on a record of pharmacy fills. To calculate adherence, glucocorticoid drug usage, based on claim records, was converted to a daily HYDRO equivalent (in mg), and adherence was measured from 6 to 12 months after the first diagnosis on record. An additional subset of patients was explored for each of the 3 main AI cohorts in patients that demonstrated both adherence more than or equal to 50% and used HYDRO as the only glucocorticoid, hereby known as the HYDRO-only subset. These sensitivity analyses were performed to ensure that cohort definitions were robust to varying degrees of drug adherence.

Statistical analysis

Every patient meeting inclusion and exclusion criteria within each AI cohort (PAI, CAH, and PIT) was matched 1:1 to a general

Table 1. Patient Demographics and Comorbidities for AI Cases and Matched Controls

	PAI		PIT		CAH	
	Case	Control	Case	Control	Case	Control
Total patients	n = 1014	n = 1014	n = 8818	n = 8818	n = 551	n = 551
Age (y)						
Mean	50.8	50.8	48.0	48.0	32.0	31.9
Median	51	51	49	49	32	32
SD	17.2	17.2	16.0	16.0	18.3	18.3
Age group (% of patients)						
<18	3.6	3.5	4.4	4.5	29.2	29.4
18–29	7.6	7.6	8.1	8.0	18.0	17.4
30–39	12.9	12.8	15.6	15.6	17.1	17.6
40–49	21.6	21.7	22.4	22.4	14.7	14.5
50–59	26.6	26.7	27.5	27.4	14.0	13.8
60–69	12.7	12.6	13.7	13.8	5.6	6.0
70–79	9.0	9.3	6.0	6.1	1.5	1.3
80+	6.0	5.8	2.3	2.3	0.0	0.0
Gender (%)						
Male	35.6	35.6	40.8	40.8	32.1	32.1
Female	64.4	64.4	59.3	59.3	67.9	67.9
Insurance coverage (%)						
Commercial	81.0	81.0	87.7	87.7	97.3	97.3
Medicare	19.0	19.0	12.3	12.3	2.7	2.7
Region (%)						
Northeast	12.3	12.3	14.6	14.6	15.4	15.4
North Central	31.0	31.0	25.7	25.7	22.5	22.5
South	33.8	33.8	43.3	43.3	43.6	43.6
West	22.4	22.4	15.3	15.3	17.6	17.6
Unknown	0.5	0.5	1.0	1.0	0.9	0.9
Comorbidity (%)						
Diabetes	18.6	11.9	20.5	12.3	18.9	6.0
Hyperlipidemia	41.5	33.6	44.5	32.3	21.6	17.4
Hypertension	43.5	35.4	51.2	34.8	31.9	21.2
Depression	45.4	26.2	44.9	24.8	29.8	19.1
Anxiety	29.8	14.3	30.7	13.8	18.9	7.8

population control group in the same insurance database (matched control). Patients were matched using the greedy algorithm based on age (within 5 y), gender, insurance type, and region (28). Summary statistics were calculated for patient demographics and key comorbid conditions by each AI cohort.

Separate logistic regression models were used to estimate the probability of having each comorbid condition (diabetes mellitus [DM], type 1 and type 2; depression; anxiety; hyperlipidemia; ad hypertension) (see Supplemental Table 2) for each AI cohort (PAI, CAH, and PIT) compared with their matched controls. For these models, covariates included year of index and patient demographics. Odds ratio (OR) and 95% confidence intervals (CIs) were used as measures of strength of association and precision, respectively.

A multivariable regression model was generated to estimate the total number of annual inpatient admissions for each AI cohort (PAI, CAH, and PIT) compared with their matched control. For this model, covariates included: year of index, patient demographics, and patient comorbidities. Kaplan Meier curves were generated to show time to inpatient admission with a primary diagnosis of infection (see Supplemental Table 3 for ICD-9 codes used to define infection).

Results

A total of 10 383 AI patients were identified in the MarketScan commercial and Medicare databases and assigned to the PAI (n = 1014), PIT (n = 8818), and CAH cohorts (n = 551) using the stated cohort definitions (Figure 1).

Baseline demographics were similar between AI and matched controls as designed (Table 1). Mean (±SD) age was lowest in the CAH group (32.0 ± 18.3 y) compared with PAI (50.8 ± 17.2 y) and PIT (48.0 ± 16.0 y), with almost 30% of CAH patients being under 18 years of age. Female gender was more frequent in comparison with male in all AI cohorts (CAH 67.9%. PAI 64.4%, and PIT 59.3%). Most patients had commercial insurance coverage (CAH 97.3%, PIT 87.7%, and PAI 81.0%).

Comorbidities

Unadjusted rates of key comorbid conditions were higher across AI patient cohorts and matched controls (see Table 1). AI patients had higher odds of all comorbid conditions of interest compared with matched controls (ranging from an OR 1.51 for hyperlipidemia in PAI and CAH patients to 3.85 for DM in CAH patients) (Table 2). The odds of having DM (type 1 or type 2) in PAI, PIT, and CAH (OR: 1.75, 1.87, and 3.85) were significantly higher compared with their respective controls. ORs for hyperlipidemia and hypertension (OR, 1.98 and 2.24) were highest in the PIT cohort. ORs for anxiety were highest in the CAH cohort (OR, 2.99; 95%CI, 2.02–4.42), whereas those for depression were highest in the PAI and PIT cohorts (OR, 2.40 and 2.55, respectively).

In an attempt to avoid confounders such as steroid type and adherence, cohort subsets examining patients with more than or equal to 50% adherence and using HYDRO only as the glucocorticoid replacement (HYDRO-only subset) were evaluated. These represented a fraction of the main 3 AI cohorts (PAI, n = 489/1014; PIT, n = 983/8818; and CAH, n = 102/551). In both adherence subsets (≥50% adherence and HYDRO), PIT patients showed higher odds of all comorbid conditions of interest compared with matched controls (each comparison based on total number of patient in the specified sample, cases in

Table 2. ORs of Comorbid Conditions in AI Cohorts and Subsets Compared With Matched Controls

Comorbid Condition	Comparison	Full AI Cohorts		AI Subset (≥50% Adherence)		AI Subset (≥50% Adherence + HYDRO-Only)	
		OR (CI)	*P* Value	OR (CI)	*P* Value	OR (CI)	*P* Value
Metabolic disorders							
DM	PAI vs controls	1.75 (1.35, 2.25)	<.0001			1.99 (1.36, 2.92)	.0004
	PIT vs controls	1.87 (1.72, 2.04)	<.0001	1.73 (1.43, 2.08)	<.0001	1.64 (1.29, 2.08)	<.0001
	CAH vs controls	3.85 (2.52, 5.90)	<.0001			7.47 (1.54, 36.22)	.0126
Hyperlipidemia	PAI vs controls	1.51 (1.23, 1.84)	<.0001			1.32 (0.98, 1.78)	.0672
	PIT vs controls	1.98 (1.84, 2.12)	<.0001	2.09 (1.77, 2.47)	<.0001	2.22 (1.80, 2.74)	<.0001
	CAH vs controls	1.51 (1.04, 2.19)	.0320			1.96 (0.52, 7.39)	.3180
Hypertension	PAI vs controls	1.53 (1.25, 1.88)	<.0001			1.36 (1.00, 1.84)	.0499
	PIT vs controls	2.24 (2.10, 2.40)	<.0001	1.69 (1.43, 1.98)	<.0001	1.51 (1.23, 1.85)	<.0001
	CAH vs controls	2.03 (1.49, 2.75)	<.0001			2.72 (0.97, 7.65)	.0584
Psychiatric disorders							
Depression	PAI vs controls	2.40 (1.97, 2.91)	<.0001			1.48 (1.12, 1.96)	.0062
	PIT vs controls	2.55 (2.38, 2.72)	<.0001	1.90 (1.62, 2.24)	<.0001	1.81 (1.47, 2.22)	<.0001
	CAH vs controls	1.89 (1.40, 2.56)	<.0001			1.93 (0.76, 4.89)	.1664
Anxiety	PAI vs controls	2.62 (2.09, 3.30)	<.0001			1.91 (1.37, 2.67)	.0001
	PIT vs controls	2.80 (2.59, 3.02)	<.0001	2.11 (1.74, 2.56)	<.0001	1.70 (1.34, 2.18)	<.0001
	CAH vs controls	2.99 (2.02, 4.42)	<.0001			1.20 (0.28, 5.09)	.8076

DM includes type 1 and type 2. See attrition diagram for total number of cases and controls.

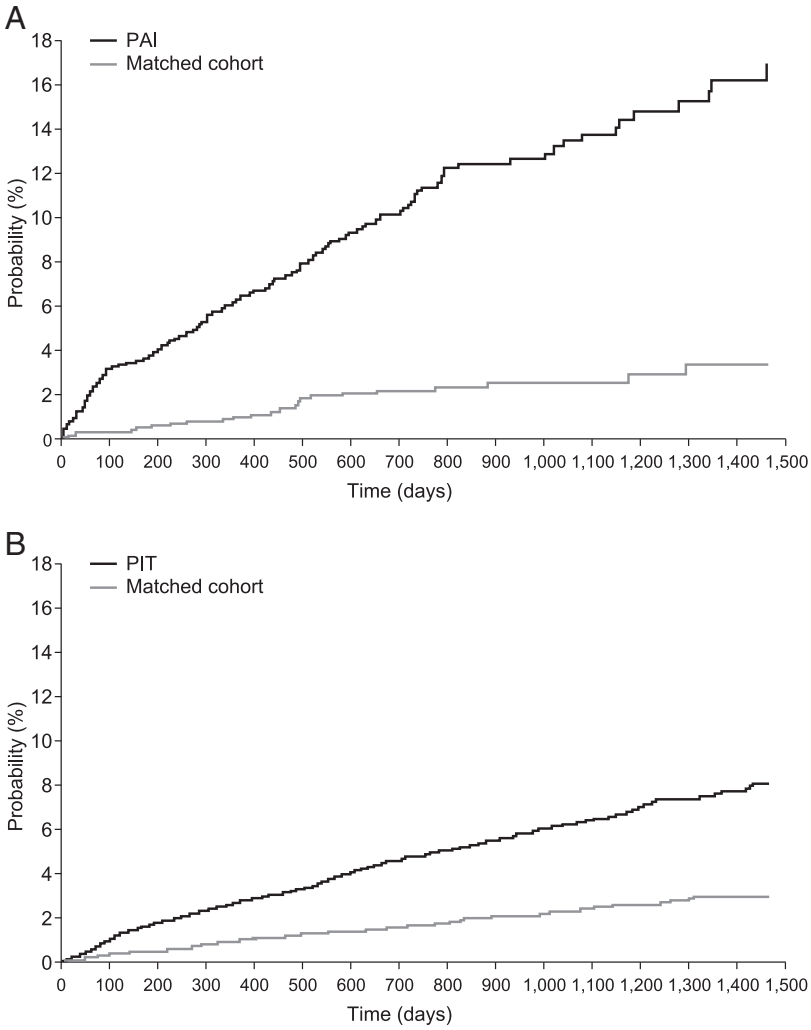

Figure 2. Probability of an inpatient admission with infection for AI cohorts: PAI cohort vs the matched control cohort (A) and secondary AI (PIT) cohort vs the matched control cohort (B).

addition to controls) (Table 2). The odds were significantly higher in the PAI HYDRO-only subset with respect to DM, depression, anxiety, and hypertension compared with their matched controls.

Hospital admissions

Inpatient admissions were more frequent in the PAI and PIT cohorts vs controls (Supplemental Table 4). For every 1 inpatient admission in the matched cohort, there were an estimated 4.64 admissions for the PAI ($P < .0001$) and 4.00 admissions for the PIT cohort ($P < .0001$). Inpatient admissions estimates were close to 0 in both the CAH cohort and its matched control group. The HYDRO-only subsets showed similar results (PAI 4.60 to 1 admissions, $P < .0001$; PIT 3.19 to 1 admissions, $P < .0001$; and CAH not applicable). The PIT more than or equal to 50% adherence subset had an estimated 4.35 inpatient admissions for every 1 control admission ($P < .0001$).

Kaplan Meier plots showing the probability of inpatient admissions with infection for the full PAI and PIT cohorts are presented in Figure 2. The largest disparity between AI and matched controls was observed in the PAI cohort, with an estimated 17% of PAI vs 3% of matched controls requiring inpatient admission with infection over a 4-year period. At the same time point, approximately 8% of PIT patients vs 3% of matched controls required inpatient admission with infection. In subsets of patients with more than 50% adherence and/or HYDRO-only, the likelihood of inpatient admissions over time was greater in both PIT subsets than in the full PIT cohort, with the more than or equal to 50% adherence PIT subset and more than or equal to 50% adherence plus HYDRO-only subset reaching an estimated 17% and 16% of patients hospitalized within 4 years, respectively (Figure 3).

Discussion

This study examines the real world "clinical care" prevalence of comorbid conditions and hospital admissions in more than 10 000 patients with AI based on insurance claims data, and incorporates patient medication adherence from pharmacy fill records. Patient comorbidities have previously been shown to be the most influential factor determining the incidence of adrenal crisis (30), a life-threatening medical emergency that is thought to account for a quarter of hospital admissions in AI patients (31). Compared with matched controls in the general population, this study showed not only an increased incidence of comorbid conditions in all AI cohorts, but also an increased rate of inpatient hospital admissions in PAI and PIT patients.

Patients diagnosed with all 3 main causes of AI (PAI, PIT, and CAH), showed increased risk of DM, depression, anxiety, hyperlipidemia, and hypertension compared with their control populations. Compared with PAI and PIT patients, CAH patients had a lower risk of depression and hospitalization. This may be influenced by the younger mean age of CAH patients related to the congenital nature of the disease. Conversely, CAH patients had the highest OR of diabetes compared with controls (OR, 3.85;

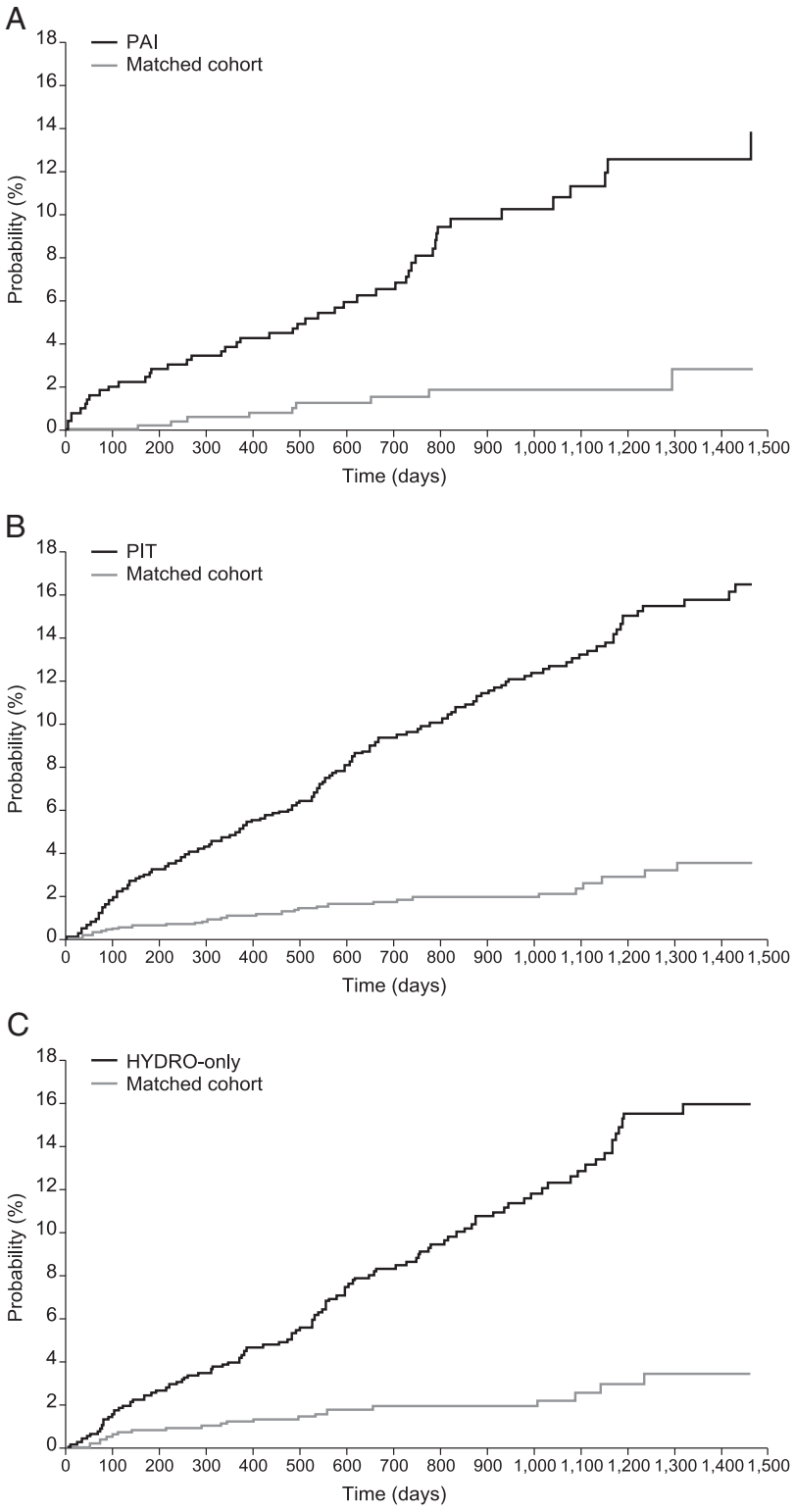

Figure 3. Probability of an inpatient admission with infection for AI subsets. A, PAI subset with both adherence of at least 50% 6–12 months after diagnosis and only receiving HYDRO (HYDRO-only). B, Secondary AI (PIT) subgroup with adherence of at least 50% 6–12 months after diagnosis. C, PIT subset with both adherence of at least 50% 6–12 months after diagnosis and HYDRO-only.

95%CI, 2.52–5.90). Previous reports have shown that DM was present in 12%–14% (13, 32) of patients with Addison's disease. The present study suggests that DM may be of greater importance in AI patients, and specifically the CAH, population than previously recognized (21, 33).

Among the many challenges with currently available AI treatment, medication compliance is considered an important issue (16). In our study, prescriptions for glucocorticoids were not filled as often as would be expected if the medication were taken as prescribed in many patients. Treatment for AI requires life-long diligence and is complicated by the need to increase glucocorticoid administration in the event of stress or illness. As such, patient education is considered to be of the utmost importance (34, 35). According to a survey of AI patients, self-reported medication compliance is suboptimal, van Eck et al reported a low patient average self-rating on dose adaptation during medical emergencies (36). Additionally, adrenal crisis is a known, serious consequence of underreplacement, yet about 90% of physicians cannot correctly identify the signs of glucocorticoid underreplacement (24, 34).

Evaluating a subset of AI patients with more than or equal to 50% adherence within this study was of significance because it made the possibility less likely that any findings would be related to inadequate daily glucocorticoid use. Generally, within the more than or equal to 50% adherence and HYDRO-only subgroup analysis, the risk of comorbid conditions was still significantly higher in the PAI and PIT populations compared with controls, although with lower ORs compared with the full AI cohorts. Similarly, PAI and PIT patients experienced significantly higher incidence of hospital admissions than the general population in both the full AI cohorts (ratio vs control; PAI 4.64, PIT 4.00) and the more than or equal to 50% adherence HYDRO-only subset analysis (ratio vs control; PAI 4.60, PIT 3.19). This demonstrates that patients with presumably good adherence to glucocorticoid replacement are still at notable health risk compared with matched control individuals (26).

Although underreplacement can be dangerous, potentially leading to adrenal crisis, chronic glucocorticoid overexposure can also lead to morbidity. Patients taking excess glucocorticoids can develop many features of Cushing's syndrome, including metabolic syndrome (17). It is now recognized that earlier isotopic methods of calculating daily cortisol secretion produced over estimates and led to recommended replacement doses that were excessive (37). It is worth noting that current recommendations to use lower daily glucocorticoid replacement doses than before still do not reproduce normal physiology (17). The diurnal pattern of cortisol release is highest in the morning and gradually declines throughout the waking day. However, AI therapy usually entails multiple daily dosing that can lead to high tissue exposure late in the afternoon and evening. Late afternoon glucocorticoid exposure has been linked to glucose intolerance, abdominal obesity, coronary atherosclerosis, and fatigue/poor sleep pattern (38–42). Because hormone replacement dosages were not collected in this study, the rate of glucocorticoid under- or overreplacement is not known. Nevertheless, based on prescription refills, patients with more than or equal to 50% adherence had a trend of numerically lower odds of comorbid conditions compared with the full AI cohort. Irrespective of adherence, PAI, PIT, and CAH patients had significant comorbidity and increased hospital admissions compared with the general population.

Limitations

The limitations of claims based data, including lack of generalizability to noninsured populations, clinical outcomes being imputed from data not prepared for research purposes, and the underreporting of certain events and diagnoses, are well known. Administrative claims data are collected for the purpose of billing and reimbursement, not for coordinating medical care or conducting outcomes research. The data are subject to coding errors and underreporting of clinical conditions, which do not trigger a billable event. This may contribute to a detection bias in which AI patients are more likely to have comorbidities recorded in comparison with the matched controls. Laboratory results and physician notes are absent, so specific medical details cannot be determined. Although prescription fills are available, such data do not reveal when or if the patient actually took the prescribed medication; likewise, physician instructions for taking medication are not available in the database and must be imputed using package size, pill dose strength, and days' supply. Finally, limitations common to all retrospective research apply: most importantly, the lack of random allocation to treatment and the absence of protocols for follow-up of all treatment cohorts, starting at a similar point in their disease course.

Despite these shortcomings, administrative data have been widely used to evaluate the association between treatments and clinical outcomes (43). Such databases can be particularly valuable for characterizing patient experience outside controlled clinical trials in rare disorders such as AI. Indeed the informatics analysis of this powerful dataset may have ramifications for determining outcomes in patients with other rare diseases.

Conclusion

This study defined 3 cohorts of AI, which included PAI, CAH, and PIT. Among all 3 cohorts, AI patients showed higher rates of metabolic and psychiatric comorbidities in comparison with matched controls. Patients with all types of AI carried a significant healthcare burden with higher risk of comorbidities and hospital admissions compared with the general population.

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