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Mortality data from the European Adrenal Insufficiency Registry—Patient characterization and associations

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Summary

Objective: Mortality from primary and secondary adrenal insufficiency (AI; PAI and SAI, respectively) is 2-3-fold higher than in the general population. Mortality relates to cardiovascular disease, acute adrenal crisis (AC), cancer and infections; however, there has been little further characterization of patients who have died.

Design/Methods: We analysed real-world data from 2034 patients (801 PAI, 1233 SAI) in the European Adrenal Insufficiency Registry (EU-AIR; NCT01661387). Baseline clinical and biochemical data of patients who subsequently died were compared with those who remained alive.

Results: From August 2012 to June 2017, 26 deaths occurred (8 PAI, 18 SAI) from cardiovascular disease (n = 9), infection (n = 4), suicide (n = 2), drug-induced hepatitis (n = 2), and renal failure, brain tumour, cachexia and AC (each n = 1); cause of death was unclear in 5 patients. Patients who died were significantly older at baseline than alive patients. Causes of AI were representative of patients with SAI; however, 3-quarters of deceased patients with PAI had undergone bilateral adrenalectomy (3 with uncontrolled Cushing's disease, 3 with metastatic renal cell cancer). There were no significant differences in body mass index, blood pressure, low-density lipoprotein cholesterol, total cholesterol or electrolytes between deceased and alive patients. Deceased patients with SAI were more frequently male individuals, were receiving higher daily doses of hydrocortisone (24.0 ± 7.6 vs 19.3 ± 5.7 mg, $P = .0016$) and experienced more frequent ACs (11.1 vs 2.49/100 patient-years, $P = .0389$) than alive patients.

Conclusions: This is the first study to provide detailed characteristics of deceased patients with AI. Older, male patients with SAI and frequent AC had a high mortality risk.

KEYWORDS

adrenal hyperplasia, adrenal insufficiency, cardiovascular diseases, cause of death, glucocorticoids, hydrocortisone, registries

1 | INTRODUCTION

If left untreated, adrenal insufficiency (AI) leads to premature death.[1] Introduction of glucocorticoid replacement therapy in patients with AI has led to greatly improved outcomes;[2] however, it is increasingly recognized that patients with AI continue to experience high levels of morbidity and premature mortality. These adverse outcomes are thought to be due to inappropriate glucocorticoid dosage and the nonphysiological nature of conventional replacement therapy.[3-5]

Hospital record data suggest that mortality associated with primary AI (PAI) is 2-3-fold higher than in the general population.[6] In the Swedish Hospital Registry, the cardiovascular mortality associated with PAI was approximately 2-fold higher, and the mortality owing to infectious disease was approximately 6-fold higher, than that of the normal population.[6] Data from the Norwegian Hospital Registry showed that, between 1943 and 2005, the mortality for PAI related mainly to cardiovascular disease, followed by Addisonian crisis, cancer, infection and sudden death.[7] More recently, the Swedish National Inpatient Register showed a dramatically reduced survival probability for patients with PAI and comorbid diabetes mellitus, compared with patients with diabetes mellitus alone. Cardiovascular disease and complications of diabetes mellitus were the most common causes of death.[8]

Patients with secondary AI (SAI) also showed an increased cardiovascular mortality.[9,10] A large, prospective study of patients with SAI in the UK demonstrated an overall standard mortality ratio (SMR) of 1.87, but could not attribute the increased mortality to any particular endocrine condition other than untreated growth hormone deficiency.[11] Analysis of a large cohort of Swedish patients with pituitary disease showed that the SMR due to infection was 6.32; all 15 individuals who died from infection (from a total of 120 deaths and 1286 patients) had SAI, and 8 of these individuals had adrenal crisis (AC). The authors concluded that AC in response to acute stress and intercurrent illness is an important cause of mortality in patients with hypopituitarism.[12] Similarly, a large cohort study in the USA demonstrated that the relative risk of death was 7.1 in patients with SAI, emphasizing the importance of early intervention when infection occurs in association with AI.[13]

There has been, however, little further characterization of the patients who died.[12] Therefore, we analysed real-world data from the European Adrenal Insufficiency Registry (EU-AIR), with centres across Germany, the Netherlands, Sweden and the UK, to further characterize the patients with AI who have died.

2 | METHODS

2.1 | Study design

European Adrenal Insufficiency Registry is an observational, open-ended study (ClinicalTrials.gov identifier: NCT01661387) of patients with PAI, SAI or congenital adrenal hyperplasia (CAH) who are undergoing long-term treatment with modified-release hydrocortisone or other glucocorticoid replacement therapies.[14] The primary objective of the EU-AIR is to monitor the safety of long-term treatment with once-daily, modified-release hydrocortisone and other glucocorticoid replacement therapies in patients with AI.

All enrolled patients provided written informed consent/assent. The study protocol was approved by the appropriate ethical committee in each country. Data were collected from endocrinology centres in Germany, the Netherlands, Sweden and the UK. All enrolled patients were followed up during the course of routine clinical practice for the active duration of the registry. All medical care decisions, including those relating to treatment choice, were entirely at the discretion of the patient and registry physician. Patient data, including laboratory assessments, were collected by means of an electronic case report form at enrolment and thereafter at routine clinic visits (every 6-12 months).[14,15]

Recruitment commenced in August 2012. Patients with CAH were excluded from this analysis. Patients who withdrew consent (n = 130) and who were lost to follow-up (n = 6) were excluded. As of June 2017, in total, 2034 patients with PAI (n = 801) and SAI (n = 1233) had been enrolled and were included in the analysis. For all included patients, follow-up data and status (deceased or alive) were available.

Exposure records with a duration of less than 28 days were excluded to ensure that treatment at baseline was not related to emergency/temporary use of medication.

Patients were grouped according to the cause of AI (PAI or SAI), and whether they had died or were still alive at the data cut-off point of June 2017. Clinical and biochemical data from the time point of study enrolment (baseline) were used.

Intercurrent illness was defined as any temporal illness where a transient increase in the glucocorticoid replacement dose is needed. Nondisease conditions, such as physical or mental stress (eg, heavy exercise), were excluded from this definition. An AC is an acute impairment of general health with the need for parenteral hydrocortisone and saline infusion. An adverse event (AE) was defined as any untoward, undesired and unplanned clinical event in the form of signs, symptoms, disease, or laboratory or physiological observations occurring in a patient participating in the clinical study, regardless of causal relationship.

2.2 | Statistics

Descriptive statistics (number of observations [N], mean, standard deviation, median, minimum, maximum and 95% confidence interval [CI] for continuous variables; incidence, percentage and 95% CI for categorical variables) were provided for the cohort of patients who had died and for the cohort of those who remained alive. Inferential comparisons were not planned; values of $P \leq .05$ indicated trends rather than tested hypotheses.

3 | RESULTS

From August 2012 until June 2017, 26 deaths occurred (8 PAI, 18 SAI) in patients enrolled in EU-AIR, resulting in a mortality of 1.0% for PAI and 1.5% for SAI. The main causes of death were cardiovascular disease (35%), infection (15%) and suicide (8%). However, for 19% of patients, the cause of death was not clear owing to the lack of documentation in the database (Table 1).

Analysis of the underlying AI aetiology for the 26 deceased patients (Table 2) demonstrated that the subgroup of patients with PAI who had died was very specific, with 6 of 8 patients having had

bilateral adrenalectomy for uncontrolled Cushing's disease (n = 3: ♀ 77 years, ♀ 64 years, ♂ 52 years) or metastatic renal cell carcinoma (n = 3: ♀ 81 years, ♂ 77 years, ♂ 55 years). Only 2 of 8 of the patients with PAI who had died had autoimmune PAI (♀ 70 years, ♂ 45 years); their causes of death were stroke and unknown cause, respectively. The time between bilateral adrenalectomy and death in patients having had bilateral adrenalectomy for uncontrolled Cushing's disease was 1.5, 9.5 and 39.5 years, and causes of death were increased intracranial pressure due to sinus thrombosis, cardiac arrhythmia and unknown cause, respectively. In patients with bilateral adrenalectomy for metastatic renal cell cancer, the cause of death was probably related to their malignancy in 2 of 3 patients (renal failure; pneumonia with underlying pulmonary metastasis). Our deceased PAI cohort therefore appears to be biased towards severely sick patients with devastating underlying disease, and we do not feel that this cohort is truly representative of patients whose primary disease is directed at the adrenal gland. These data must therefore be interpreted with caution. The fact that the primary disease may have been fundamentally more important in the deceased PAI cohort is supported by the lower number of AEs and ACs, compared with the cohort of patients with PAI who remained alive (Table 3). In the cohort of alive patients with PAI, the frequency of AC was 7.94 per 100 patient-years (Table 3).

TABLE 1 Causes of death in 26 patients (8 primary adrenal insufficiency, 18 secondary adrenal insufficiency) occurring between August 2012 and June 2017 in the European Adrenal Insufficiency Registry

Cause of death	N
Cardiovascular	9
Heart failure, arrhythmia	7
Stroke	1
Sinus thrombosis	1
Unclear (general physical health deterioration)	5
Infection	4
Gastroenteritis	2
Fever	1
Pneumonia	1
Suicide	2
Toxic drug hepatitis	2
Brain tumour	1
Acute adrenal crisis	1
Renal failure	1
Cachexia	1

The underlying aetiology for AI in the patients with SAI who died (Table 2) represents the common causes of SAI observed within specialized endocrine centres. In the cohort of patients with SAI who died, we observed a tendency towards more AEs and a significantly higher number of ACs compared with the SAI cohort who remained alive (Table 3).

In general, at baseline, patients who died were older than the average age of those who remained alive (PAI, 65.1 ± 13.3 vs 48.0 ± 16.0 years, $P = .003$; SAI, 64.2 ± 17.5 vs 54.2 ± 16.2 years, $P = .009$). In addition, patients who died were more likely to have been diagnosed with hypertension (PAI, 75.0% vs 19.9%, $P = .0001$; SAI, 77.8% vs 33.6%, $P = .0001$) and diabetes mellitus (PAI, 62.5% vs 13.4%, $P = .0001$; SAI, 27.8% vs 10.6%, $P = .02$).

There were no significant differences in body mass index, systolic or diastolic blood pressure, or levels of LDL cholesterol, high-density lipoprotein cholesterol, total cholesterol, serum potassium or serum sodium between the patients who died and those who

TABLE 2 Underlying causes of AI in deceased patients with AI; data from the European Adrenal Insufficiency Registry

Primary AI	N = 8
Bilateral adrenalectomy due to pituitary Cushing's disease	3
Bilateral adrenalectomy due to metastatic renal cell carcinoma	3
Autoimmune primary AI	2
Secondary AI	**N = 18**
Panhypopituitarism due to:	7
Empty sellae, Sheehan's syndrome	2
Pituitary surgery for adenoma	3
Pituitary surgery for craniopharyngioma	1
meningioma	1
Panhypopituitarism and diabetes insipidus due to:	3
Pituitary surgery for adenoma	1
Pituitary surgery for craniopharyngioma	1
Pituitary surgery for pineal germinoma	1
Of unknown origin	5
Due to exogenous glucocorticoids	3

AI, adrenal insufficiency.

TABLE 3 Frequency of adverse events and adrenal crises in patients with PAI and SAI who died or remained alive

	PAI			SAI		
	Dead (n = 8)	Alive (n = 793)	*P* value	Dead (n = 18)	Alive (n = 1215)	*P* value
Number of adverse events per patient	2.6 ± 1.6	5.7 ± 10.7	.0004	3.5 ± 4.6	2.9 ± 5.7	.6753
	2.0	2.0		1.5	0.0	
	(1; 5)	(0; 119)		(0; 16)	(0; 72)	
Number of adrenal crises per 100 patient-years	0	7.94	—	11.1	2.49	.0389

PAI, primary adrenal insufficiency; SAI, secondary adrenal insufficiency; SD, standard deviation.
Data given as mean ± SD, median (range) for continuous variables, and percentage for categorical variables.

TABLE 4 Duration of disease and characteristics of glucocorticoid replacement therapy in patients with who died or remained alive

	PAI			SAI		
	Dead (n = 8)	Alive (n = 793)	*P* value	Dead (n = 18)	Alive (n = 1215)	*P* value
Duration of disease, years	10.7 ± 12.9	18.0 ± 14.4	.1490	16.5 ± 13.8	13.6 ± 11.1	.2683
	7.5	15.0		12.2	11.7	
	(0.3, 39.6)	(0.0, 70.3)		(0, 42.6)	(0.0, 77.7)	
Type of glucocorticoid, %[a]						
Cortisone acetate	0	2.3	—	11.1	4.4	—
Dexamethasone	0	4.5		0	0	
Hydrocortisone	87.5	77.0		83.3	88.4	
MR-HC	0	11.1		0	3.6	
Prednisolone	12.5	7.6		5.6	3.8	
Daily dose, mg/day						
Cortisone acetate	—	30.6 ± 6.5	—	31.3 ± 8.8	25.5 ± 6.9	.2550
Dexamethasone	—	0.3 ± 0.2	—	—	—	—
Hydrocortisone	25.7 ± 7.3	23.1 ± 9.4	.4591	24.0 ± 7.6	19.3 ± 5.7	.0016
MR-HC	—	25.1 ± 5.7	—	—	20.1 ± 3.1	—
Prednisolone	5.0	5.4 ± 2.1	—	5.0	5.3 ± 2.1	—
Fludrocortisone daily dose, mg/day	0.1 ± 0.02	0.1 ± 0.04	.0798	—	—	—
Proportion of patients on DHEA, %	12.5	8.3	.7274	0	3.1	.4387
Statin therapy, %	12.5	11.9	.9829	33.3	22.5	.3118
L-thyroxine treatment, %	50	41.2	.7239	84.2	83.9	1.0
Sex hormone replacement, %	12.5	9.8	.5659	47.4	50.5	1.0
Growth hormone treatment, %	—	—	—	36.8	39.9	1.0

DHEA, dehydroepiandrosterone; MR-HC, modified-release hydrocortisone; PAI, primary adrenal insufficiency; SAI, secondary adrenal insufficiency; SD, standard deviation.
[a]Some patients took glucocorticoid combinations, therefore, the sum can be more than 100%.
Data given as mean ± SD, median (range) for continuous variables, and percentage for categorical variables.

remained alive (both PAI and SAI cohorts). HbA_{1c} levels were higher in the patients with PAI who died than in those who remained alive (6.7 ± 0.6% vs 5.7 ± 0.9%, *P* = .01); however, no difference was observed in the SAI cohorts (deceased vs living: 6.2 ± 1.3% vs 5.6 ± 0.8%, *P* = .16).

In the SAI cohort, patients who died were predominantly male (77.8% vs 51.5%, *P* = .0269), whereas no difference was observed in the PAI cohort. Importantly, patients with SAI who died had been on higher daily doses of hydrocortisone (24.0 ± 7.6 vs 19.3 ± 5.7 mg, *P* = .002), but showed no significant differences regarding the use of dehydroepiandrosterone replacement or statins (Table 4). There was no significant difference in medication usage (L-thyroxine, sex hormone replacement or growth hormone replacement) between patients who died and those who remained alive (Table 4).

4 | DISCUSSION

This is the first prospective study investigating causes of death in patients with AI. The major cause of death was cardiovascular disease, confirming hospital registry data from Norway for patients with PAI.[7] The second most frequent cause was unclear (general physical health deterioration), raising the question that an illness with an inappropriately low or zero adaptation of glucocorticoid medication might have led to this. In the Norwegian Hospital Registry, "sudden death" was the fifth most frequent cause of death for patients with PAI.[7] One of the major causes of death in our study was infection (15%), whereas Addisonian crisis was only documented once. This is consistent with recent data which showed impaired immune function in patients with AI.[16] From a clinical point of view, and including the evidence that there is a "point of no return" with some AC, it appears to be appropriate to combine these 2 causes together, which would result in AC/infections being the cause of death in 19.2% of patients with AI. Of particular note, however, are the 2 suicides. This observation is endorsed by a recent study which showed suicide to account for 10% of all causes of death in patients with CAH.[17] This raises the question of patient concern over the implications of their disease,[18] which might not have been adequately addressed by medical personnel.

Our data show that it is very important to analyse the underlying aetiology of AI. In our cohort of patients with PAI who died, 3-quarters had a bilateral adrenalectomy owing to either renal cell cancer (3/8) or uncontrolled Cushing's disease (3/8); only 2 of 8 patients had autoimmune PAI. Therefore, data for the patients with PAI who died are not representative of patients with autoimmune PAI and cannot be compared with cohorts of patients with autoimmune PAI. Nevertheless, this demonstrates that patients who underwent bilateral adrenalectomy for these 2 causes have an increased risk owing to their comorbidities (either metastatic renal cell cancer or Cushing's disease, with often insufficiently treated cortisol excess over a longer period with all related comorbidities). The low number of AEs and ACs in this group supports the greater influence of their comorbidities.

The patients with SAI who died represent typical groups of patients with SAI who are managed in specialized endocrine centres. Importantly, we observed a tendency towards more AEs and a significantly higher number of ACs in the patients with SAI who died compared with the living cohort. With 11.1 ACs per 100 patient-years in the patients with SAI who died, this rate is high compared with other cohorts of patients with SAI who have reported rates of 3.2-5.8 ACs per 100 patient-years[19-21] and resembles more closely the rate of AC observed in PAI cohorts (5.2-9.3 ACs per 100 patient-years).[19-24] Additionally, we did not find a difference in the frequency of administration of hormone replacement therapy for the other pituitary axes (L-thyroxine medication, sex hormone and growth hormone replacement therapy) between patients with SAI who died and those that remained alive. Therefore, we believe that our cohort of patients with SAI, which consisted mainly of male, older individuals who had a higher prevalence of hypertension and diabetes mellitus, is a high-risk group which deserves further attention and care. We suggest that the significantly higher, daily hydrocortisone dose in this cohort reflects the response of the treating physician to increase the hydrocortisone dosage when these patients have repeated AEs and ACs on standard, low doses of glucocorticoid therapy.

Interestingly, a recently published study based on a national inpatient database in Japan revealed that patients with SAI and AC were admitted to the intensive care unit more frequently and received extracellular fluid resuscitation, insulin therapy and catecholamines at a higher frequency than patients with PAI and AC.[25] The authors concluded that older patients with impaired consciousness and diabetes mellitus had a higher risk of death from AC.

It has been suggested that older patients with AI might have psychological and cognitive difficulties that impair self-management of their AI, especially the use of stress doses[26] and parenteral administration of hydrocortisone in emergency situations. Social isolation, which is more frequent in older age groups, might also play a role. Additionally, older patients often show no typical symptoms of infectious disease, such as fever, and thereby delay self-management of the necessary hydrocortisone dose increases or delay approaching emergency medical personnel for parenteral application of glucocorticoids.

It is important to emphasize that our study is not representative of all European AI patients but of European AI patients who are treated in specialized centres with highly specialized care (eg, regular patient teaching sessions are common), and a high proportion of rare cases (eg, bilateral adrenalectomized Morbus Cushing patients).

We cannot rule out a certain selection bias in our study due to the fact that follow-up information was not available for patients who withdrew consent (n = 130) and those patients were not included in our cohort. Also, we cannot exclude death in patients who have been lost to follow-up (n = 6), and who similarly were not included in the analysis.

In conclusion, we have shown for the first time, the characteristics of patients with AI who have died. We identified older, male patients with SAI, who also have hypertension and diabetes mellitus as comorbidities, as having a high frequency of AC and a high mortality risk. We conclude that this high-risk group deserves further attention and increased care.

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CONFLICT OF INTEREST

Marcus Quinkler, Bertil Ekman, Andrea M. Isidori and Robert D. Murray received honoraria for talks and consultancy from Viropharma/Shire. Pinggao Zhang is an employee of Shire.

AUTHOR CONTRIBUTIONS

All authors contributed to the conception of the work; the acquisition, analysis and interpretation of the data; and drafting and revision of the manuscript. All authors meet the International Committee of Medical Journal Editors criteria for authorship for this manuscript, take responsibility for the integrity of the work as a whole and have given final approval of the version to be published.

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