JOURNAL OF INSURANCE MEDICINE

J Insur Med 2025;00:000–000

Comparative Mortality in Adrenal Insufficiency Patients

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Objective.—This article presents an analysis of mortality data in individuals with a diagnosis of adrenal insufficiency compared to a matched population from a United Kingdom database.

Background.—Adrenal insufficiency is an easily treated disease, but if undiagnosed and/or glucocorticoid stress dosing is not appropriately implemented at times of illness, then death may occur.

Methods.—Tabular data on patients with primary and secondary adrenal insufficiency relative to matched controls was generated using the pixel method on the all-cause mortality graph published in the Ngaosuwan et al study.

Results.—Calculated annual mortality rates, excess death rates, and interval mortality rates were higher for both primary and secondary adrenal insufficiency compared to matched controls. And the increased mortality risk appeared to be greater in those with primary adrenal insufficiency compared to those with secondary adrenal insufficiency.

Conclusion.—Those with primary and secondary adrenal insufficiency have increased mortality compared to their matched cohort, especially in the early years after their diagnosis.

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Key words: Adrenal insufficiency, Addison's disease, primary adrenal insufficiency, secondary adrenal insufficiency.

Received: January 2, 2025

Accepted: February 11, 2025

OBJECTIVE

The objective of this article is to present the mortality risk of primary adrenal insufficiency and secondary adrenal insufficiency, respectively, to matched controls, based on a United Kingdom (UK) general practitioner database cohort of patients.

BACKGROUND

The adrenals are a pair of triangular-shaped endocrine glands located superior medial to the kidneys that produce life-sustaining hormones, including cortisol.[1] Adrenal insufficiency develops when there is inadequate glucocorticoid production from the adrenal cortex, either because of a lack of regulatory stimulation or an inherent adrenal failure. Primary adrenal insufficiency (PAI), also known as Addison's disease, is a rare condition, which also includes inadequate aldosterone production. Secondary adrenal insufficiency (SAI) is due to pituitary adrenocorticotropic hormone (ACTH) stimulation insufficient to maintain physiologic cortisol production by the adrenal glands. Tertiary adrenal insufficiency is due to insufficient hypothalamic corticotropin-releasing hormone stimulation from the anterior pituitary, thereby leading to inadequate ACTH stimulation and subsequent cortisol deficiency.[1,2]

Before the discovery of corticosterone and the clinical use of hydrocortisone, PAI was fatal.[3] Since Thomas Addison described the clinical signs and symptoms of adrenal insufficiency via several case presentations in 1855[4]

and the standardization of confirmatory diagnostic adrenal stimulation testing with cosyntropin,[5,6] those with adrenal insufficiency can live healthy lives once the disease is diagnosed and appropriate treatment started. However, disease symptoms can be subtle, and without high clinical suspicion, the diagnosis of adrenal insufficiency can still be missed, leading to morbidity and death without timely treatment, especially at times of increased physiologic stress.[2] Prevalence of primary, secondary, and tertiary adrenal insufficiency are all increasing.[7] Secondary and tertiary adrenal insufficiency are on the rise due to exogenous glucocorticoid therapy prescribed for other diagnoses requiring sustained steroid treatment for anti-inflammatory effects. This prolonged prescription use may cause iatrogenic hypothalamic-pituitary-adrenal (HPA) axis suppression. In those with secondary and tertiary adrenal insufficiency, the effects may be transient with eventual recovery of the HPA axis, but until normalization of the axis occurs, physiologic glucocorticoid doses are needed to keep the individual well.

There is a paucity of data investigating mortality risk in those with adrenal insufficiency. The study by Ngaosuwan et al analyzes mortality risk in this cohort of patients with primary and secondary adrenal insufficiency compared to a matched reference population.[8] In this study, the authors obtained data from the Clinical Practice Research Datalink, a general practitioner UK-based database of 734 practices from 1987 to 2017. The diagnosis of adrenal insufficiency was based on medical diagnosis codes in conjunction with oral glucocorticoid prescriptions documented within 3 months of the diagnosis codes in those younger than 100 years old. Exclusions included specific diagnoses (Cushing disease, Cushing syndrome, congenital adrenal hyperplasia, malignancy of adrenal or pituitary glands) or a follow-up period of less than 1 month. Those with PAI (n=2052) were analyzed separately from those with SAI (n=3948), and they were each compared with 20,366 and 39,134 controls, respectively, individually matched for sex, age, geographic location and period of care. Median follow-up was 4.6 years for PAI and 4.4 years for SAI with 4.3 and 4.0 years for their respective matched controls.[8]

METHODS

Using the "pixel method,"[9] annual mortality data (Table 1) was generated from the all-cause mortality graph from the Ngaosuwan et al study in patients with primary and secondary adrenal insufficiency relative to matched controls. From the original study, the control groups for primary and secondary adrenal insufficiency were treated as a single curve, since they were essentially superimposed on the graph. Once the mortality data for the 2 impairment groups (PAI and SAI) and the comparison group were obtained, the mortality ratio (MR) and excess death rate (EDR) for the impairments were calculated for the annual intervals (Tables 2 and 3) and for multi-year intervals of 0–5 years, 5–10 years and 0–10 years (Tables 4 and 5).

RESULTS

Mortality rates were higher for PAI, particularly in year 1 (0.0565) and year 2 (0.0453), compared to matched controls in year 1 (0.0276) and year 2 (0.0194) as shown in Table 1. SAI also showed an increased mortality rate compared to matched controls in year 1 (0.0440) and year 2 (0.0329), but the increased mortality was more pronounced for PAI, relative to SAI. Starting at year 3, the mortality rates for PAI plateaued at a rate comparable to SAI. However, both primary and secondary adrenal insufficiency had higher mortality rates compared to matched controls for all years, as seen in Table 1.

This data trend of higher mortality was more obvious when looking at the excess death rates (EDRs) for year 1 (28.89) and year 2 (25.89), compared to year 3 (10.84) and later for PAI as demonstrated in Table 2. The same relatively higher EDR compared to

Table 1. Annual Mortality Data for Primary Adrenal Insufficiency and Secondary Adrenal Insufficiency Compared to Matched Controls

	Primary Adrenal Insufficiency				Secondary Adrenal Insufficiency				Controls			
	Mortality Rates		Survival Rates		Mortality Rates		Survival Rates		Mortality Rates		Survival Rates	
Year	Interval q	Cumulative Q	Interval p	Cumulative P	Interval q	Cumulative Q	Interval p	Cumulative P	Interval q’	Cumulative Q’	Interval p’	Cumulative P’
0	0	0	1	1	0	0	1	1	0	0	1	1
1	0.0565	0.0565	0.9435	0.9435	0.0440	0.0440	0.9560	0.9560	0.0276	0.0276	0.9724	0.9724
2	0.0453	0.0992	0.9547	0.9008	0.0329	0.0754	0.9671	0.9246	0.0194	0.0465	0.9806	0.9535
3	0.0293	0.1256	0.9707	0.8744	0.0313	0.1043	0.9688	0.8957	0.0184	0.0641	0.9816	0.9359
4	0.0345	0.1558	0.9655	0.8442	0.0295	0.1307	0.9705	0.8693	0.0188	0.0817	0.9812	0.9183
5	0.0313	0.1822	0.9688	0.8178	0.0246	0.1520	0.9754	0.8480	0.0178	0.0980	0.9822	0.9020
6	0.0353	0.2111	0.9647	0.7889	0.0237	0.1721	0.9763	0.8279	0.0153	0.1118	0.9847	0.8882
7	0.0223	0.2286	0.9777	0.7714	0.0288	0.1960	0.9712	0.8040	0.0184	0.1281	0.9816	0.8719
8	0.0277	0.2500	0.9723	0.7500	0.0266	0.2173	0.9734	0.7827	0.0173	0.1432	0.9827	0.8568
9	0.0302	0.2726	0.9698	0.7274	0.0289	0.2399	0.9711	0.7601	0.0176	0.1583	0.9824	0.8417
10	0.0242	0.2902	0.9758	0.7098	0.0182	0.2538	0.9818	0.7462	0.0179	0.1734	0.9821	0.8266

matched controls for SAI was seen for years 1–4 (Table 3).

The increased mortality risk persists in those with PAI, although to a lesser degree when comparing the interval 0–5 years to the interval 5–10 years (Table 4). For PAI specifically, the mortality was 0.1822 for the interval 0–5 years, compared to 0.1321 for the interval 5–10 years. This pattern holds true for SAI, although again, to a lesser extent when comparing the same intervals of 0–5 years (0.1520) and 5–10 years (0.1200) as shown in Table 5. For the interval 5–10 years, the mortality risk for primary and secondary adrenal insufficiency was comparable at 0.1321 and 0.1200, respectively (Tables 4 and 5). The difference between primary and secondary adrenal insufficiency appears to be related to early years after initial diagnosis, with PAI having more pronounced risk of death early after diagnosis.

CONCLUSION

The purpose of this article was to assess the mortality of those with primary and secondary adrenal insufficiency. When rating an individual with adrenal insufficiency for life insurance coverage, it is important to recognize that those with adrenal insufficiency are at increased mortality risk, especially in the early years after their diagnosis. This suggests that an individual’s knowledge and understanding of their disease impacts hospitalizations and eventual mortality, although the risk of mortality does not completely dissipate over time. Thus, an individual with longstanding adrenal insufficiency who has consistent medical care, routine vaccinations to prevent severe illness, and has good understanding of their adrenal insufficiency, would be expected to have lower mortality and would support a lower life rating, compared to someone who is repeatedly hospitalized with episodes of adrenal crisis due to non-adherence to their medical treatment and/or severe illness.

The strengths of the study include a large sample size with cohort comparison from a

Table 2. Comparative Experience for Annual Intervals for Primary Adrenal Insufficiency

Excess Death Rate (per thousand) Interval	Year	Mortality Ratio (%)		Survival Ratio (%)	
		Interval	Cumulative	Interval	Cumulative
	0				
28.89	1	204.55	204.55	97.03	97.03
25.89	2	233.61	213.51	97.36	94.47
10.84	3	158.79	196.08	98.90	93.42
15.69	4	183.50	190.77	98.40	91.93
13.47	5	175.72	185.90	98.63	90.67
20.01	6	230.61	188.76	97.97	88.83
3.91	7	121.24	178.43	99.60	88.47
10.40	8	160.12	174.56	98.94	87.54
12.56	9	171.36	172.22	98.72	86.42
6.27	10	135.00	167.39	99.36	85.87

database, with matching for age, sex, geographical location and period of care. But there are limitations in extrapolating this UK-based adrenal insufficiency population to adrenal insufficiency populations worldwide, including Asian and African countries, where incidence of adrenal insufficiency differs. Furthermore, healthcare access and delivery vary across countries, which may influence diagnosis, timeliness of treatment and mortality for adrenal insufficiency.[11-12]

Additionally, although Ngaosuwan et al did match for geographical location between the study population and the cohort, the authors did not specifically account for socioeconomic status. Matching for geographical location may only account indirectly for socioeconomic status. Socioeconomic disparity could also be an important factor in chronic management of adrenal insufficiency, as it is relevant in other chronic disease outcomes.[13]

Despite adrenal insufficiency disease recognition and treatment availability for more than 150 years, this article indicates that there is an increased mortality risk in those with adrenal insufficiency in this UK-specific population.

Table 3. Comparative Experience for Annual Intervals for Secondary Adrenal Insufficiency

Excess Death Rate (per thousand) Interval	Year	Mortality Ratio (%)		Survival Ratio (%)	
		Interval	Cumulative	Interval	Cumulative
	0				
16.33	1	159.09	159.09	98.32	98.32
13.47	2	169.51	162.16	98.63	96.97
12.80	3	169.42	162.75	98.70	95.70
10.66	4	156.73	160.00	98.91	94.66
6.78	5	138.14	155.13	99.31	94.01
8.38	6	154.72	153.93	99.15	93.21
10.44	7	156.80	152.94	98.94	92.22
9.27	8	153.62	151.75	99.06	91.35
11.30	9	164.21	151.59	98.85	90.30
0.27	10	101.52	146.38	99.97	90.27

Table 4. Primary Adrenal Insufficiency Multiyear Mortality Data Compared to Control Population

Primary Adrenal Insufficiency						Control	Comparison
Interval	q	Q	p	P	Mortality Geometric Average Annual q^{V}	Mortality Geometric Average Annual $q^{V'}$	Mortality Ratio Geometric Average Annual MR
0–5 years	0.1822	0.1822	0.8178	0.8178	0.0394	0.0204	1.93
5–10 years	0.1321	0.2902	0.8679	0.7098	0.0279	0.0173	1.61
0–10 years	0.2902	0.2902	0.7098	0.7098	0.0337	0.0189	1.79

Table 5. Secondary Adrenal Insufficiency Multiyear Mortality Data Compared to Control Population

Secondary Adrenal Insufficiency						Control	Comparison
Interval	q	Q	p	P	Mortality Geometric Average Annual q^{V}	Mortality Geometric Average Annual $q^{V'}$	Mortality Ratio Geometric Average Annual MR
0–5 years	0.1520	0.1520	0.8480	0.8480	0.0324	0.0204	1.59
5–10 years	0.1200	0.2538	0.8800	0.7462	0.0252	0.0173	1.46
0–10 years	0.2538	0.2538	0.7462	0.7462	0.0288	0.0189	1.53

The completion of this paper would not have been possible without the support of the Mortality and Morbidity Committee. Special thanks to Dr. Steven Rigatti for his guidance and valuable feedback.

REFERENCES

1. Kumar R, Wassif WS. Adrenal insufficiency. *J Clin Pathol*. 2022;75:435–442. doi:10.1136/jclinpath-2021-207895
2. Husebye ES, Pearce SH, Krone NP, Kämpe O. Adrenal insufficiency. *Lancet*. 2021;397:613–629. doi:10.1016/S0140-6736(21)00136-7
3. Barthel A, Benker G, Berens K, et al. An Update on Addison's Disease. *Exp Clin Endocrinol Diabetes*. 2019;127:165–175. doi:10.1055/a-0804-2715
4. Addison T. *On the Constitutional and Local Effects of Diseases of The Supra-Renal Capsules*. London: Warren and Son; 1855.
5. Rothwell PM, Udwadia ZF, Lawler PG. Cortisol response to corticotropin and survival in septic shock. *Lancet*. 1991;337:582–583. doi:10.1016/0140-6736(91)91641-7
6. Khare S, Anjum F. Adrenocorticotropic Hormone (Cosyntropin) Stimulation Test. In: *StatPearls*. Treasure Island (FL): StatPearls Publishing; 2023.
7. Rushworth RL, Torpy DJ. The Changing Epidemiology of Adrenal Insufficiency: Iatrogenic Factors Predominate. *J Endocr Soc*. 2023;7:bvad017. doi:10.1210/jendso/bvad017
8. Ngaosuwan K, Johnston DG, Godsland IF, et al. Increased Mortality Risk in Patients With Primary and Secondary Adrenal Insufficiency. *J Clin Endocrinol Metab*. 2021;106:e2759–e2768. doi:10.1210/clinem/dgab096
9. Rigatti SJ. A simple method for computer-based survival curve measurement. *J Insur Med*. 2009;41:107–109.
10. Gunna S, Singh M, Pandey R, et al. Etiology, clinical characteristics and mortality among Indian patients with Addison's disease. *Endocr Connect*. 2023;12:e220439. doi:10.1530/EC-22-0439
11. Mofokeng TRP, Beshyah SA, Ross IL. Characteristics and Challenges of Primary Adrenal Insufficiency in Africa: A Review of the Literature. *Int J Endocrinol*. 2022;2022:8907864. doi:10.1155/2022/8907864
12. Kibirige D, Owarwo N, Kyazze AP, et al. Prevalence, Clinical Features, and Predictors of Adrenal Insufficiency in Adults With Tuberculosis or HIV: A Systematic Review and Meta-analysis. *Open Forum Infect Dis*. 2024;11:ofae098. doi:10.1093/ofid/ofae098
13. Pillay-van Wyk V, Bradshaw D. Mortality and socioeconomic status: the vicious cycle between poverty and ill health. *Lancet Glob Health*. 2017;5:e851–e852. doi:10.1016/S2214-109X(17)30304-2