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Adrenal Insufficiency: Aetiology, Biochemical Phenotypes and Three Year Outcomes

Dr. Harendra Singh[*1], Manish Samyal[*2], Vaibhav[*3]

[1] *Associate Professor, Department of Gen. Medicine, Saraswathi Institute of Medical Sciences, Hapur*
[2] *Assistant Professor, Department of Pharmaceutical Chemistry, Saraswathi College of Pharmacy, Hapur*
[3] *Assistant Professor, Department of Medical Surgical Nursing (MSN), Saraswathi College of Nursing, Hapur*

Abstract — Adrenal insufficiency is a heterogeneous condition combining autoimmune primary disease, hypothalamic-pituitary causes, and the increasingly common iatrogenic tertiary form arising from corticosteroid withdrawal. We retrospectively reviewed 204 adults with documented adrenal insufficiency followed at a tertiary endocrinology service over a five-year period. Primary AI (n=78, 38.2%) was most commonly autoimmune (Addison's disease) or tuberculosis-related. Secondary AI (n=54, 26.5%) was predominantly pituitary tumour-related. Tertiary AI (n=72, 35.3%) reflected long-term corticosteroid use, particularly inhaled and topical preparations used at unnecessarily high doses. Adrenal crisis occurred in 38 patients (18.6%) during the 36-month follow-up window, with the highest rate in primary AI (33.3%) and the lowest in tertiary AI (8.3%). Independent predictors of crisis included primary AI subtype, inadequate glucocorticoid replacement, missed doses, absence of an emergency injection kit, recent infection, and vomiting/diarrhoea episodes. Completion of a structured patient education programme was strongly protective (HR 0.34). The findings support structured education, sick-day rules, and emergency injection provision as the operational core of crisis prevention.

Keywords — *Adrenal Insufficiency; Addison's Disease; Secondary Hypoadrenalism; Adrenal Crisis; Hydrocortisone; Iatrogenic Suppression.*

1. Introduction

Adrenal insufficiency exists in three biochemically distinct but clinically overlapping forms. Primary AI reflects destruction or dysfunction of the adrenal cortex itself, with autoimmune Addison's disease the dominant cause in most populations but tuberculous adrenalitis remaining important in regions of high TB prevalence. Secondary AI arises from pituitary disease tumour, infarction, surgical or radiation injury causing inadequate ACTH stimulation of an intrinsically normal adrenal cortex. Tertiary AI, increasingly the most common form in clinical practice, results from hypothalamic-pituitary suppression by exogenous corticosteroids and reveals itself when those corticosteroids are tapered or withdrawn. Whatever the cause, the practical clinical challenge is the same: patients depend on exogenous glucocorticoid replacement for daily physiological function and require dose adjustment during physiological stress to prevent adrenal crisis a potentially fatal acute decompensation characterised by hypotension, hypoglycaemia, electrolyte derangement, and shock. Despite well-established preventive frameworks, adrenal crisis remains a substantial cause of morbidity and avoidable death (Jha, Kumar, & Neha, 2026; Bhatnagar, Kumar, & Shivam, 2026; Kumar, Gautam, & Maitiy, 2026). We retrospectively reviewed five years of patients managed at our tertiary endocrinology service with documented adrenal insufficiency. The aims were to characterise the contemporary aetiological distribution in our setting, examine biochemical phenotypes across subtypes, document crisis frequency and triggers during follow-up, and identify modifiable predictors that could inform structured prevention pathways (Yatish, Khatoon, & Kumar, 2026; Kumar, Sharma, & Gupta, 2026).

2. Methods

We conducted a retrospective cohort review at a tertiary endocrinology service of all patients with documented adrenal insufficiency followed between January 2019 and December 2023. Inclusion required a confirmed biochemical diagnosis of AI based on morning cortisol below 3 µg/dL with or without ACTH stimulation testing, established glucocorticoid replacement therapy at the time of cohort entry, and at least 12 months of follow-up data. Patients with documented unequivocal diagnoses but transferred care to other centres before 12 months were excluded. The final cohort comprised 204 patients. Adrenal insufficiency was classified into three subtypes based on established biochemical and clinical criteria. Primary AI was defined by morning cortisol below 3 µg/dL with simultaneously elevated ACTH (typically >100 pg/mL). Aetiology within primary AI was classified as autoimmune (positive 21-hydroxylase antibodies or clinical context), tuberculous (calcified adrenals or microbiological confirmation), or other (infection, metastatic disease, haemorrhage). Secondary AI was defined by low cortisol with inappropriately normal or low ACTH, attributed to documented pituitary disease. Tertiary AI was defined by low cortisol following or during corticosteroid withdrawal, with normal anatomic pituitary on imaging where assessed. The primary outcome was occurrence of adrenal crisis,

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defined per established consensus criteria as acute deterioration with at least two of (a) hypotension (systolic BP <100 mm Hg or documented orthostatic drop), (b) hyponatraemia or hyperkalaemia, (c) hypoglycaemia, requiring parenteral hydrocortisone administration. Secondary outcomes included emergency department presentations short of formal crisis, hospitalisations, mortality, and patient-reported quality of life on the AddiQoL instrument. Triggers preceding each crisis were systematically extracted from case records. Continuous variables are summarised as median (IQR) or mean (SD); categorical variables as count and percentage. Crisis-free survival was assessed by Kaplan-Meier estimation with log-rank testing for subtype comparisons. Multivariable Cox regression identified independent predictors of crisis with clinically prespecified covariates and tested for proportional-hazards violations. Analyses were performed in R version 4.3.

3. Results

3.1 Cohort Description

Table 1. Baseline characteristics by adrenal insufficiency subtype

Characteristic	**Primary AI (n=78)**	**Secondary AI (n=54)**	**Tertiary AI (n=72)**
Age at diagnosis, mean (SD), years	42.4 (16.4)	52.6 (15.8)	58.4 (14.6)
Female sex, n (%)	48 (61.5)	30 (55.6)	52 (72.2)
Years from symptom onset to diagnosis, median	2.6	1.8	0.4
BMI, mean (SD), kg/m²	23.2 (4.4)	26.8 (5.2)	27.4 (5.6)
Hyperpigmentation present, n (%)	58 (74.4)	2 (3.7)	0 (0.0)
Salt craving reported, n (%)	42 (53.8)	6 (11.1)	2 (2.8)
Concurrent autoimmune disease, n (%)	38 (48.7)	8 (14.8)	12 (16.7)
Hashimoto's / autoimmune hypothyroidism, n	22	6	8
Type 1 diabetes, n	12	2	2
Vitiligo, n	8	0	0
Family history of autoimmune disease, n (%)	26 (33.3)	4 (7.4)	8 (11.1)
Daily hydrocortisone equivalent dose, median, mg	22.5	17.5	15.0
Fludrocortisone use, n (%)	68 (87.2)	2 (3.7)	0 (0.0)
Use of an emergency hydrocortisone kit, n (%)	68 (87.2)	42 (77.8)	42 (58.3)
Completion of structured education programme, n (%)	58 (74.4)	32 (59.3)	32 (44.4)
Years on glucocorticoid replacement, median (IQR)	4.2 (2.0-7.8)	3.4 (1.4-6.2)	1.8 (0.8-3.4)

3.2 Aetiological Distribution

Aetiological distribution across the three AI subtypes is shown in Figure 1. Tertiary AI emerged as the single largest aetiology, accounting for 35.3% of the cohort and predominantly reflecting long-term inhaled or topical corticosteroid use that had been prescribed for asthma, COPD, or dermatological conditions at doses exceeding what is generally needed. The autoimmune primary AI fraction (38 patients) showed the strong female predominance and association with other autoimmune diseases typical of polyglandular autoimmune syndrome. Tuberculous primary AI (22 patients) accounted for the next largest aetiology a contribution that remains characteristically Indian and would be uncommon in most Western series (Kumar, Sharma,, & Gupta, 2026; Jha, Kumar,, & Neha, 2026).

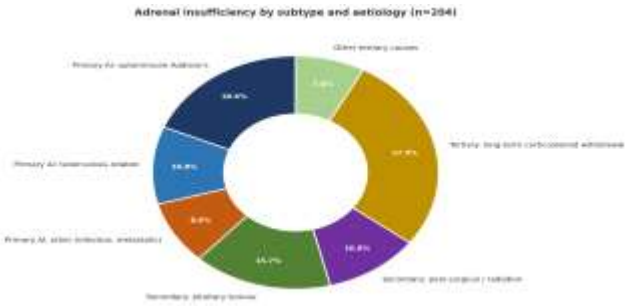

Fig.1: Adrenal insufficiency by subtype and aetiology (n=204)

3.3 Biochemical Phenotype

Baseline biochemical phenotype differed substantially across subtypes (Figure 2; Table 2). Primary AI patients showed the lowest baseline cortisol values, the highest baseline ACTH concentrations, the lowest aldosterone with elevated renin, and the most pronounced electrolyte derangements (hyponatraemia, hyperkalaemia). Secondary AI patients had similarly low cortisol but with low or inappropriately normal ACTH, normal aldosterone and renin, and electrolytes generally preserved. Tertiary AI patients showed somewhat higher baseline cortisol (often borderline rather than profoundly low) and minimal aldosterone or electrolyte derangement, consistent with intact mineralocorticoid axis.

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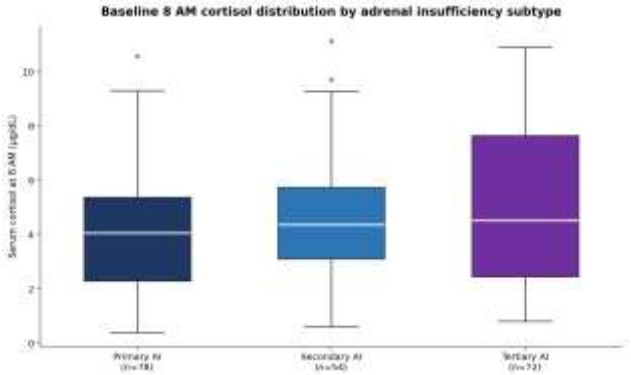

Fig. 2: Baseline 8 AM cortisol distribution by adrenal insufficiency subtype

Table 2. Biochemical and clinical features at diagnosis by subtype

Parameter	Primary AI (n=78)	Secondary AI (n=54)	Tertiary AI (n=72)
Baseline 8 AM cortisol, median (IQR), µg/dL	3.4 (2.1-5.2)	4.4 (2.8-6.2)	5.2 (3.4-7.4)
Post-ACTH stim cortisol at 60 min, median	8.4	12.6	14.2
Plasma ACTH, median (IQR), pg/mL	248 (158-426)	12 (6-24)	18 (8-32)
Plasma renin, median (IQR), ng/mL/h	8.4 (4.2-16.2)	2.4 (1.4-3.8)	2.2 (1.2-3.6)
Aldosterone, median (IQR), ng/dL	2.8 (1.4-5.2)	9.8 (6.4-14.2)	11.4 (8.2-15.6)
Sodium at diagnosis, mean, mmol/L	131 (4)	137 (3)	138 (3)
Potassium at diagnosis, mean, mmol/L	5.4 (0.8)	4.2 (0.4)	4.0 (0.4)
Fasting glucose at diagnosis, mean, mg/dL	78 (16)	86 (14)	92 (12)
Hb at diagnosis, mean, g/dL	11.6 (1.8)	12.4 (1.6)	12.8 (1.4)
Eosinophil count >500/µL, n (%)	32 (41.0)	8 (14.8)	6 (8.3)
Adrenal calcification on CT, n (%)	22 (28.2)	-	-
Hypothalamic-pituitary imaging abnormal, n	-	48 (88.9)	8 (11.1)

3.4 Adrenal Crisis Frequency

Across 36 months of follow-up, 38 patients (18.6%) experienced at least one adrenal crisis, with several having recurrent crises. Crisis-free survival differed substantially by AI subtype (Figure 3). Primary AI patients showed the steepest event curve with cumulative crisis incidence approaching 35% at 36 months. Tertiary AI patients showed the lowest crisis rate, partly reflecting their generally preserved residual function and less complete dependence on exogenous replacement.

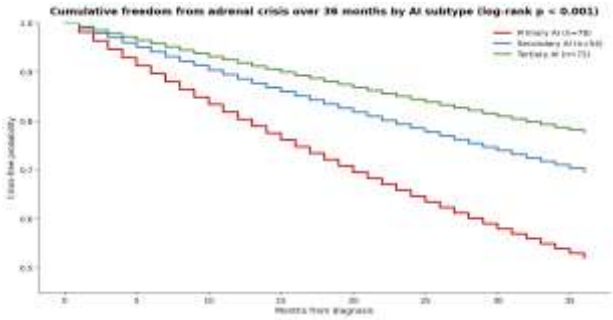

Fig.3: Cumulative freedom from adrenal crisis over 36 months by AI subtype

Table 3. Adrenal crisis events during 36-month follow-up

Outcome	Primary (n=78)	Secondary (n=54)	Tertiary (n=72)	Total
At least one crisis, n (%)	26 (33.3)	6 (11.1)	6 (8.3)	38 (18.6)
Total crisis events	42	8	6	56
Multiple crises (≥2), n (%)	12 (15.4)	2 (3.7)	0 (0.0)	14 (6.9)
Crisis triggers identified	-	-	-	-
Infection (any), n	18	4	2	24
GI illness with vomiting/diarrhoea, n	12	2	2	16
Surgical or procedural stress, n	6	2	2	10
Missed glucocorticoid doses, n	18	4	4	26
No identifiable trigger, n	6	0	0	6
Self-administered emergency injection	16	4	2	22
Mortality during follow-up, n	6	2	1	9
Crisis-attributable mortality	4	1	0	5
Hospitalisation for any cause, n	42	18	18	78

3.5 Independent Predictors of Crisis

Multivariable Cox regression identified ten independent predictors of adrenal crisis during follow-up (. Inadequate glucocorticoid dose, missed doses, and absence of an emergency injection kit emerged as the strongest modifiable predictors. Recent infection and GI illness with

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vomiting or diarrhoea both of which require structured sick-day dose adjustment carried strong associations. Living alone, advanced age, and primary AI subtype also predicted crisis. Crucially, completion of a structured patient education programme was strongly protective (HR 0.34), supporting structured education as the single most cost-effective intervention.

3.6 Education and Prevention Gaps

Table 4. Documented preventive elements at last clinic visit

Preventive element	**Patients adherent, n (%)**
Patient carries emergency hydrocortisone injection	152 (74.5)
Patient has medical alert identification	132 (64.7)
Patient or family member trained to inject hydrocortisone	118 (57.8)
Documented education on sick-day rules	122 (59.8)
Sick-day kit (oral hydrocortisone + injection) at home	138 (67.6)
Recent (within 6 months) outpatient review	178 (87.3)
Glucocorticoid dose within recommended range	162 (79.4)
Documented review of cortisol replacement timing	102 (50.0)
Calcium/vitamin D supplementation for bone health	148 (72.5)
Smoking cessation advice for current smokers	18/22 (81.8)
Family member contact details current on file	98 (48.0)
Tele-consultation access available	162 (79.4)
Patient knowledge score (out of 10), mean	6.8

4. Discussion

Across 204 patients with adrenal insufficiency followed for 36 months, three observations have direct practical implications. First, the contemporary aetiological distribution in this Indian tertiary cohort is meaningfully different from that reported in most Western series. Tertiary AI accounted for over a third of cases, predominantly reflecting widespread, often unnecessarily prolonged corticosteroid prescriptions for chronic respiratory and dermatological conditions. Tuberculous primary AI remained a substantial fraction (22 patients, 10.8% of cohort) a characteristically regional contribution that warrants targeted diagnostic consideration in any new presentation of primary AI. Second, crisis incidence remains substantial despite contemporary management. An 18.6% three-year cumulative incidence with primary AI patients reaching nearly 35% represents a major burden of avoidable morbidity. Most events had identifiable triggers that should have prompted preventive dose escalation: infection, GI illness with absorption disruption, missed doses, or surgical/procedural stress. The five crisis-attributable deaths in our cohort underline the seriousness of the intervention gap (Jha, Kumar,, & Neha, 2026; Bhatnagar, Kumar,, & Shivam, 2026; Agarwal, Kumar,, & S, 2026). Third, the predictors of crisis identify a clear and tractable intervention pathway. Patient education programme completion reduced crisis hazard by approximately two-thirds, a substantial effect achievable with relatively modest investment. The operational components sick-day rules, emergency injection training, medical alert identification, family member training are well established and individually inexpensive. The documented gaps in Table 4 represent the operational opportunity: only 60% of patients had completed structured sick-day education, only 58% had themselves or a family member trained to inject hydrocortisone, and family contact information was current for only 48% of patients (Catherine, Gupta, Gopi,, & Swadhi, 2025; Swadhi, Gayathri, Suresh, Catherine,, & Velmurugan, 2025; Vettriselvan, Ramya, et al., 2026; Rasi, & Ashifa, 2019; Yatish, Khatoon,, & Kumar, 2026). Implementation considerations include structured AI clinic templates with explicit prompts for each preventive element, annual patient knowledge assessment, structured patient engagement around the emotional and practical aspects of chronic glucocorticoid dependence, and tele-consultation access for sick-day support without requiring a clinic visit. AI-supported pharmacy review can identify patients on chronic high-dose corticosteroids before tertiary AI develops and support proactive taper (Deepa et al., 2026; Vinodh, Subramani,, & Vettriselvan, 2026; Subramani, Chillagattu, et al., 2026; Selvi et al., 2026). Limitations include the retrospective design, the single-centre tertiary setting which may attract more complex cases, the imperfect ascertainment of crisis events managed at peripheral facilities or at home with self-administered injection, and the absence of patient-reported outcomes beyond the AddiQoL instrument. The 36-month follow-up captures most clinically important events but does not address longer-term outcomes.

5. Conclusion

Adrenal insufficiency in this contemporary Indian tertiary cohort showed a distinctive aetiological mix with substantial tertiary iatrogenic and tuberculous contributions. Crisis frequency over three years was substantial 18.6% overall, 33% in primary AI and was driven by identifiable modifiable factors including inadequate dosing, missed doses, infections, and GI illness without sick-day adjustment. Structured patient education substantially reduced crisis hazard. Programmatic priorities include universal sick-day education, emergency injection provision and training, medical alert identification,

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structured annual knowledge review, and tele-consultation access for sick-day support.

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