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ORIGINAL ARTICLE

Diagnostic Value of Key Clinical Characteristics and Baseline Cortisol in Assessing Adrenal Function in Patients Receiving Glucocorticoid Therapy

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Abstract

Background. Prolonged glucocorticoid therapy may result in multi-organ complications and adrenal insufficiency (AI). To mitigate these risks, clinicians typically taper and discontinue treatment once the underlying disease is controlled. Prior to withdrawal, adrenal function is assessed through dynamic testing. However, dynamic testing often requires multiple blood samples for cortisol measurement, continuous patient monitoring for several hours, and close supervision by medical staff throughout the procedure to assess potential adverse effects. In addition, dynamic tests are typically costly and not all healthcare facilities are equipped to perform such procedures.

Objective. Evaluate the diagnostic performance of baseline cortisol and clinical parameters in the assessment of adrenal insufficiency.

Methodology. Cross-sectional study of 96 patients on prolonged glucocorticoid treatment at Nguyen Tri Phuong hospital. Insulin tolerance test (IST) was the gold standard for diagnosis of adrenal insufficiency.

Results. Among 96 patients, 56 (58.3%) had AI. A positive correlation was observed between baseline cortisol levels and peak cortisol levels during the insulin tolerance test, demonstrating a moderately strong association (r = 0.62, p <0.001). Baseline cortisol had good diagnostic performance, with areas under the receiver operating characteristic curve (AUROC) of 0.83 [95% confidence interval (CI): 0.78-0.89]. If the optimal cutoff value for morning serum cortisol is set at 9.0 µg/dL, the test demonstrates a sensitivity of 69% and a specificity of 67%. We observed that the morning serum cortisol cutoff of 3 µg/dL had a positive predictive value (PPV) of 100% and the morning serum cortisol cutoff of 15 µg/dL had a negative predictive value (NPV) of 100%. Among the predictive models for AI, the model incorporating baseline characteristics such as Cushingoid appearance, duration of glucocorticoid therapy, history of hypertension, and baseline cortisol demonstrated the highest predictive accuracy, with an AUC of 0.87 (95% CI: 0.80-0.94).

Conclusion. The assessment of baseline cortisol in conjunction with baseline characteristics offers a reliable method for predicting the risk of adrenal insufficiency, thereby minimizing the necessity for expensive and intricate dynamic testing. In circumstances where dynamic testing is not feasible due to limitations in resources, cost, or expertise, we advocate for the implementation of a model that incorporates baseline characteristics and cortisol levels. This approach provides a practical, cost-effective solution for evaluating adrenal function, requiring only a single blood sample and ensuring broader accessibility.

Key words: Adrenal insufficiency, glucocorticoid therapy, baseline cortisol level, insulin tolerance test, predictive model

INTRODUCTION

Adrenal insufficiency is a life-threatening condition that may be caused by primary adrenal insufficiency or secondary adrenal insufficiency due to suppression of the hypothalamic-pituitary-adrenal axis. The prevalence of secondary adrenal insufficiency is estimated to be approximately 150-280 cases per million people, with a higher prevalence in females compared to males.[1,2] Among the etiologies of secondary adrenal insufficiency, the use of exogenous glucocorticoids is the most prevalent cause.[1,3] A systematic review and meta-analysis reported a 48.7% risk of secondary adrenal insufficiency in patients using oral glucocorticoids, 7.8% with inhaled glucocorticoids, 4.7% with topical glucocorticoid application, and 4.2% with intranasal glucocorticoids. The highest risk, 52.2%, was

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observed in patients receiving intra-articular glucocorticoid injections.[4] The widespread overuse of glucocorticoids in Vietnam stemming from their easy accessibility and broad availability poses a significant clinical concern. In addition to over-the-counter use, these agents are commonly prescribed by specialists for various conditions. Prolonged glucocorticoid therapy may result in multi-organ complications and suppression of the hypothalamic-pituitary-adrenal (HPA) axis, leading to adrenal insufficiency. To mitigate these risks, clinicians typically taper and discontinue treatment once the underlying disease is controlled. Before ceasing glucocorticoids, adrenal function should be assessed through dynamic testing to ensure that the risk of adrenal insufficiency is low, thereby allowing for the safe discontinuation of glucocorticoid therapy.[5] In Vietnam, dynamic tests commonly employed to evaluate adrenal function include the Synacthen stimulation test and the insulin tolerance test. Both procedures necessitate multiple blood draws for cortisol measurement and require continuous patient monitoring over a period of one to two hours. These tests must be conducted under strict medical supervision by the endocrinologist and nursing staff to ensure patient safety and to promptly identify any adverse effects. Moreover, the implementation of dynamic testing is challenged by high costs and the limited availability of essential reagents, such as Synacthen, within the local healthcare system. Furthermore, not all medical institutions are adequately equipped to perform these specialized procedures, and non-endocrinologist physicians often lack experience in conducting dynamic tests. Therefore, we questioned whether a simpler and more practical test could replace complex dynamic testing procedures, allowing physicians regardless of specialty to assess adrenal function before safely discontinuing glucocorticoid therapy.

According to the 2024 clinical guidelines of the European Society of Endocrinology and the Endocrine Society, dynamic testing is no longer routinely recommended for diagnosing adrenal insufficiency (AI) in patients who are tapering or discontinuing glucocorticoid therapy.[6] The current clinical practice trend favors the selection of common, inexpensive static tests with simple procedures, offering sensitivity and specificity approaching those of dynamic tests. In this regard, baseline cortisol levels measured 24 hours after the final dose of glucocorticoid are of significant value in assessing the risk of adrenal insufficiency in patients.[6]

Currently, there is no established model or scoring system for assessing the risk of adrenal insufficiency resulting from long-term glucocorticoid therapy. Therefore, our study was conducted with the objective to evaluate the diagnostic value of baseline cortisol level in detecting adrenal insufficiency and to develop a model that integrates clinical features with baseline cortisol level, aiming to assess the risk of adrenal insufficiency associated with long-term glucocorticoid use and to facilitate its application in routine clinical practice.

METHODOLOGY

Study design

This cross-sectional study was conducted at Nguyen Tri Phuong Hospital, a state hospital located in Ho Chi Minh City, Vietnam, from May 2023 to February 2024. The hospital provides both secondary and tertiary care services, receiving patients from within the city as well as referrals from lower-level healthcare facilities in surrounding regions. The hospital primarily serves an urban population with diverse clinical presentations. Patients were recruited based on specific inclusion and exclusion criteria, and all participants underwent the insulin tolerance test (ITT) to assess adrenal function before discontinuing glucocorticoids. Data collection included baseline characteristics, clinical features, underlying conditions, glucocorticoid treatment regimens, the baseline cortisol and serum cortisol levels during the ITT.

Eligibility criteria

Inclusion criteria included patients aged 18 and above with a history of intake of prednisolone greater than or equal to 5 mg per day or methylprednisolone greater than or equal to 4 mg per day, on a daily or alternate-day basis for at least 2 weeks and baseline cortisol levels between 3 and 17 μg/dL.

Exclusion criteria included patients using glucocorticoids for less than 2 weeks, those with baseline cortisol levels greater than or equal to 18 μg/dL or less than 3 μg/dL, night shift workers, pregnant women, patients with a history of epilepsy, coronary artery disease, cerebrovascular disease, cirrhosis with albumin less than 25 g/L, those on glucocorticoid therapy for acute conditions, or those taking estrogen-containing medications, neuropsychiatric medications or neuroleptics.

Baseline characteristics included age, gender, height, weight. Clinical features collected included Cushingoid appearance and glucocorticoid withdrawal syndrome. Underlying conditions indicated for glucocorticoid treatment, comorbidities and characteristics of glucocorticoid treatment are also collected. At the first visit, if the patient met the inclusion criteria and did not violate any exclusion criteria, we asked them to stop taking glucocorticoids for at least two days and scheduled another day for an 8:00 AM serum cortisol test. If the 8:00 AM serum cortisol fell between 3 and 17 μg/dL, we scheduled another day for an insulin tolerance test in the morning at 8:00 AM, and the patient had to ensure they had discontinued glucocorticoids for at least two days before undergoing the insulin tolerance test. Patients who met the inclusion criteria were required to discontinue glucocorticoid treatment for at least 2 days prior to undergoing the ITT. The test was started by intravenous injection of 0.1 to 0.15 UI/kg body weight insulin (Insulin Actrapid Human) to induce hypoglycemia. The patients remained supine and were constantly supervised by an experienced nurse and

doctor. Test quality was defined as adequate only if the plasma blood glucose was less than or equal to 2.2 mmol/L, regardless of the presence or absence of hypoglycemic symptoms. The patient must be alert and able to answer questions, with monitoring of hypoglycemic symptoms and capillary blood glucose every 5-15 minutes. When the blood glucose was less than or equal to 2.2 mmol/L, management depended on the severity of hypoglycemia and the serum cortisol levels were measured at 0 minutes, 30 minutes, 60 minutes, 90 minutes, 120 minutes after insulin injection. Adrenal function was classified according to the highest cortisol level (peak cortisol). A peak serum cortisol level greater than or equal to 18 μg/dL following the insulin tolerance test (ITT) was considered indicative of normal adrenal function, whereas a peak cortisol level less than 18 μg/dL was diagnosed as adrenal insufficiency. If the blood glucose was greater than 2.2 mmol/L after 30 minutes, we repeated the same insulin dose and continued monitoring hypoglycemic symptoms and capillary blood glucose every 5 to 15 minutes until the target hypoglycemia was reached. If the target blood glucose was not achieved after two insulin injections, the test was discontinued. During the data cleaning process, patients who did not meet the inclusion criteria or met any of the exclusion criteria were removed from the study. In addition, those who declined to participate in our study, refused to undergo the insulin tolerance test, or had contraindications to the procedure were also excluded. Furthermore, patients with missing data on key variables – such as baseline cortisol levels, clinical parameters relevant to the predictive model, or insulin tolerance test results - were excluded from the final analysis.

Sample size

Based on a systematic review and meta-analysis of 30 studies (4), the prevalence of adrenal insufficiency in patients using oral glucocorticoids is estimated at 48.7%. The sample size was calculated using the formula:

$$N = \frac{Z_{(1-\alpha/2)}^2 \times [P(1-P)]}{d^2} = \frac{1.96^2 \times 0.487 \times (1-0.487)}{0.1^2} = \frac{0.9597}{0.01} = 96$$

Where:
N : sample size
z_α : Confidence level 0.95 and $z_{1-\alpha/2} = 1.96$
P : population proportion = 0.487
d : margin error with d = 0.1

Laboratory methods

The baseline cortisol levels in this study were measured using the Chemiluminescent Microparticle Immunoassay (CMIA) method, performed on the Architect system developed by Abbott, USA. The Laboratory Department of Nguyen Tri Phuong Hospital has been certified by the Ho Chi Minh City Center for External Quality Assessment in Medical Laboratory.

Statistical methods

Data were entered into Excel and analyzed using Stata software. Continuous variables with a normal distribution were presented as mean ± standard deviation (SD). Continuous variables without a normal distribution were expressed as median and interquartile range (IQR). Categorical variables were reported as percentages.. The diagnostic values of baseline cortisol levels included sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). Receiver Operating Characteristic (ROC) curve analysis was performed to evaluate the diagnostic performance of baseline cortisol levels, using the insulin tolerance test as the reference standard for assessing adrenal function. A peak serum cortisol level ≥18 μg/dL following the insulin tolerance test (ITT) was considered indicative of normal adrenal function, whereas a peak cortisol level <18 μg/dL was diagnostic of adrenal insufficiency.

Predictive models for adrenal insufficiency were constructed utilizing readily obtainable and clinically pertinent baseline characteristics along with baseline cortisol levels, using logistic regression models. Due to the limited sample size, we selected nine clinical characteristics based on their potential in terms of clinical usage and statistical significance (p <0.2 from univariable analyses). We then built a model including all nine clinical variables (model #1), then used stepwise backward to reduce the number of variables (model #2). For model #3 we added baseline cortisol to model #2. Finally we built a model with baseline cortisol as the only covariable (model #4) to see how it performed. The discriminative ability and predictive performance of each model were evaluated using the area under the receiver operating characteristic curve (AUC). Significance was determined according to p <0.05.

Ethics

Ethics approval was obtained from the Ethics Committee of Nguyen Tri Phuong Hospital. Patients were informed about the study and had the right to consent or decline participation. All related testing costs were covered, and data confidentiality was maintained.

RESULTS

During the study period, a total of 96 patients met the inclusion criteria and were enrolled in the study. Among them, 74 were female (77.1%) with a mean age of 47.5 ± 14.3 years. There were no statistically significant differences in age, sex, weight, height, BMI, waist circumference, or blood pressure between the adrenal insufficiency and non-adrenal insufficiency groups. As our sample collection was primarily conducted in three clinics: Rheumatology, Otorhinolaryngology, and Endocrinology, the analysis results showed that the majority of underlying conditions indicated for glucocorticoid treatment were rheumatoid arthritis at 31.3%, followed by lupus at 23.9%, pharyngitis

Table 1. Baseline characteristics of participants

Characteristics	Total, N = 96
Gender, n (%)	
Female	74 (77.1%)
Male	22 (22.9%)
Age, years Mean ± SD = 47.5 ± 14.3	
Underlying conditions indicated for glucocorticoid, n (%)	
Rheumatoid arthritis	30 (31.3%)
Lupus	23 (23.9%)
Pharyngitis	18 (18.8%)
Exogenous Cushing syndrome	9 (9.4%)
Sinusitis	4 (4.2%)
Otitis media	3 (3.1%)
Dermatomyositis	2 (2.2%)
Sjogren syndrome	1 (1.0%)
Nephrotic syndrome	3 (3.1%)
Knee osteoarthritis	1 (1.0%)
Lumbar disc herniation	1 (1.0%)
Sciatic nerve pain	1 (1.0%)
Clinical characteristics of patients on glucocorticoid, n (%)	
Abdominal obesity	23 (24.0%)
Thin skin with easy bruising	15 (15.6%)
Fatigue	13 (13.5%)
Exhaustion	11 (11.5%)
Loss of appetite	11 (11.5%)
Moon face	9 (9.4%)
Cataracts	8 (8.3%)
Dizziness	4 (4.2%)
Abdominal or thigh striae	4 (4.2%)
Nausea and vomiting	5 (5.2%)
Buffalo hump	3 (3.1%)
Neuropsychiatric symptoms	3 (3.1%)
Comorbidities of patients on glucocorticoid, n (%)	
Dyslipidemia	38 (39.6%)
Hypertension	29 (30.2%)
Gastritis	28 (29.2%)
Osteoporosis	19 (19.8%)
Diabetes mellitus	12 (12.5%)
Neuropsychiatric disorders	9 (9.4%)

Mean ± SD: Mean ± Standard Deviation

at 18.8%, exogenous Cushing's syndrome at 9.4%, sinusitis at 4.2% and the remaining conditions accounted for 12.4%. Most clinical symptoms commonly observed in patients on glucocorticoid therapy were abdominal obesity at 24%, thin skin with easy bruising at 15.6%, fatigue at 13.5%, exhaustion and loss of appetite at 23%, and moon facies at 9.4%. The rest were attributed to other symptoms. Comorbidities among patients receiving glucocorticoid therapy were diverse. Dyslipidemia was the most frequently reported comorbidity, affecting 39.6% of patients. This was followed by hypertension (30.2%), gastritis (29.2%), osteoporosis (19.8%), diabetes mellitus (12.5%), and neuropsychiatric disorders (9.4%) (Table 1). Comparing the two groups, the adrenal insufficiency group had greater number of patients with comorbidities compared to the non-adrenal insufficiency group, but this difference was not statistically significant (Table 3).

All patients were receiving glucocorticoid therapy as prescribed by physicians in the outpatient clinic. The treatment protocol is presented in Table 2. The entire study population was treated with either methylprednisolone or prednisolone and were receiving maintenance doses, as their underlying conditions had been stabilized.

Given that the underlying diseases were stable, glucocorticoid tapering and discontinuation were considered in order to minimize the risk of AI. All patients underwent ITT to assess adrenal function. Baseline cortisol levels and cortisol levels response at various time points following the test are presented in Table 3. After performing the ITT, we determined that the prevalence of adrenal insufficiency was 58.3%, while the non-adrenal insufficiency group accounted for 41.7%.

Figure 1 illustrates a statistically significant positive correlation between baseline cortisol levels and the peak cortisol response during the insulin tolerance test (ITT), with a correlation coefficient of r = 0.62 (p <0.001), indicating a moderately strong association. Receiver operating characteristic (ROC) analysis identified multiple cut-off values of baseline cortisol, each associated with corresponding sensitivity and specificity, in the prediction of AI. The ROC curve was generated using a peak cortisol response greater than 18 μg/dL as the reference standard for normal adrenal function. The area under the curve (AUC) was 0.83 (95% CI: 0.78–0.89), indicating good diagnostic accuracy (Figure 2).

Based on the morning cortisol cutoff points derived from the ROC curve, we determined the diagnostic performance of the optimal cortisol cutoff value according to Youden's Index, as shown in Table 4.

Predictive models for adrenal insufficiency were constructed utilizing readily obtainable and clinically pertinent clinical characteristics along with baseline cortisol

Table 2. Baseline characteristics between the adrenal insufficiency and no adrenal insufficiency groups

	All (N = 96)	No adrenal insufficiency (N = 40)	Adrenal insufficiency (N = 56)	*P* value
Age (years), Mean ± SD	47.5 ± 14.3	46.0 ± 14.1	48.6 ± 14.5	0.384
Gender: n (%)				0.219
Female	74 (77.1%)	28 (70.0%)	46 (82.1%)	
Male	22 (22.9%)	12 (30.0%)	10 (17.9%)	
Weight (kg), Mean ± SD	57.5 ± 10.4	57.0 ± 11.2	57.9 ± 9.9	0.695
Height (cm), Mean ± SD	158 ± 7	159 ± 7	158 ± 7	0.645
BMI (kg/m²), Mean ± SD	22.9 ± 3.6	22.5 ± 3.7	23.1 ± 3.5	0.438
Systolic blood pressure (mmHg), Mean ± SD	116.5 ± 14.3	117.7 ± 15.5	115.6 ± 13.4	0.501
Diastolic blood pressure (mmHg), Mean ± SD	71.3 ± 10.5	73.0 ± 12.0	70.0 ± 9.3	0.180

Mean ± SD: Mean ± Standard Deviation

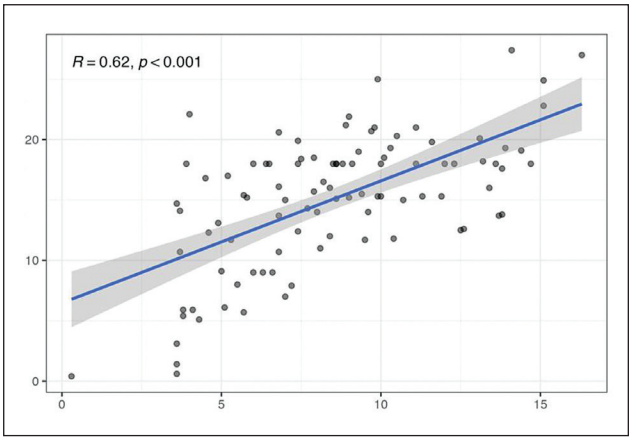

Figure 1. Correlation between baseline cortisol and peak cortisol levels during the insulin tolerance test.

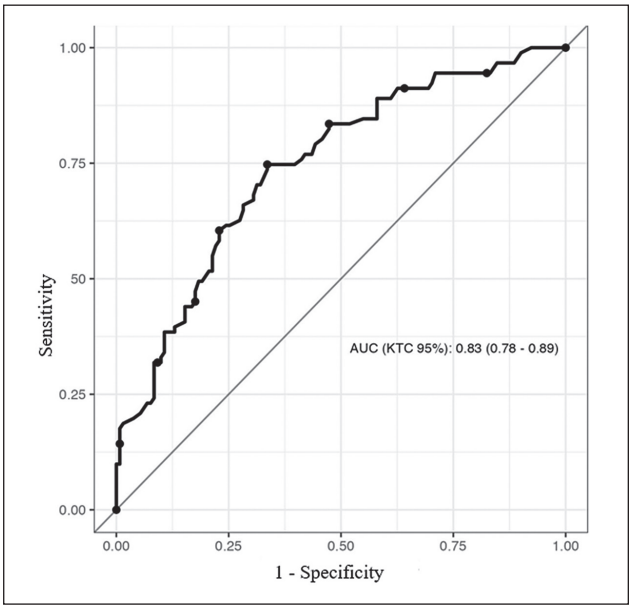

Figure 2. Receiver operating characteristic (ROC) curve illustrating the predictive performance of baseline cortisol levels for adrenal insufficiency.

levels. These models were designed to facilitate early identification of adrenal dysfunction. In Model 1, clinical factors were selected based on two criteria: (1) potential association identified through univariate analysis (p <0.2), and (2) established clinical significance. Accordingly, nine variables were included: age, sex, dyslipidemia, hypertension, osteoporosis, total duration of glucocorticoid treatment, abdominal obesity, moon facies, and cataracts. The diagnostic performance of this model for adrenal insufficiency was good, with an area under the receiver operating characteristic curve (AUC) of 0.81. In Model 2, to streamline the predictive model, we performed a stepwise backward elimination based on statistical significance thresholds. Starting from the full set of variables included in Model 1, variables were sequentially removed if they did not contribute significantly to the model's predictive power. This process resulted in the identification of three key clinical predictors: hypertension, total duration of glucocorticoid treatment, and moon facies. Consistent with Model 1, Model 2 also demonstrated an AUC of 0.81. Model 3 was developed by integrating the key clinical predictors identified in Model 2 with baseline cortisol levels to enhance the prediction of adrenal insufficiency risk. This combined model demonstrated superior diagnostic accuracy, achieving an area under the curve (AUC) of 0.87, thereby outperforming both preceding models. Model 4, based solely on baseline cortisol levels, demonstrated the lowest diagnostic accuracy compared to the other models, with an AUC of 0.75 (Table 5).

DISCUSSION

Among the 96 patients included, the mean age was 47.5 ± 14.3 years. A predominance of female participants was noted, comprising 77.1% of the cohort. In our study, the higher proportion of female patients may be due to autoimmune and musculoskeletal diseases being more common in women than in men. Additionally, women tend to use healthcare services more frequently than men, including for the diagnosis and treatment of chronic diseases. This

Table 3. Comorbidities of patients between the adrenal insufficiency and no adrenal insufficiency groups

	All (N = 96)	No adrenal insufficiency (N = 40)	Adrenal insufficiency (N = 56)	*P* value
Comorbidities, n (%)				
Dyslipidemia	38 (39.6%)	11 (27.5%)	27 (48.2%)	0.057
Hypertension	29 (30.2%)	8 (20.0%)	21 (37.5%)	0.075
Gastritis	28 (29.2%)	12 (30.0%)	16 (28.6%)	0.999
Osteoporosis	19 (19.8%)	5 (12.5%)	14 (25.0%)	0.194
Diabetes mellitus	12 (12.5%)	3 (7.5%)	9 (16.1%)	0.348
Psychiatric disorders	9 (9.4%)	4 (10.0%)	5 (8.9%)	0.999

Table 4. Characteristics of glucocorticoid treatment

	All (N = 96)	No adrenal insufficiency (N = 40)	Adrenal insufficiency (N = 56)	*P* value
Type of glucocorticoid, n (%)				0.541
methylprednisolone	49 (51.0%)	22 (55.0%)	27 (48.2%)	
prednisolone	47 (49.0%)	18 (45.0%)	29 (51.8%)	
Glucocorticoid dose, (mg) MED (IQR)	5 (4; 5)	5 (4; 8)	5 (4; 5)	0.022
Total duration of treatment, (months) MED (IQR)	8 (2; 17)	3 (1; 9)	12 (6; 24)	<0.001

MED (IQR): Median (Interquartile Range)

Table 5. Cortisol levels during the insulin tolerance test

	All (N = 96)	No adrenal insufficiency (N = 40)	Adrenal insufficiency (N = 56)	*P* value
Cortisol level (mcg/dL), MED (IQR)				
Baseline cortisol level	8.4 (6.0; 10.6)	9.9 (8.3; 12.5)	6.9 (5.0; 9.4)	<0.001
Cortisol T0 (mcg/dL)	8.3 (5.8; 10.6)	9.8 (7.8; 12.1)	6.8 (5.1; 9.1)	<0.001
Cortisol T30 (mcg/dL)	8.1 (5.6; 11.4)	10.9 (8.0; 12.8)	6.7 (4.9; 8.6)	<0.001
Cortisol T60 (mcg/dL)	15.3 (11.0; 18.0)	18.4 (18.0; 20.8)	11.8 (7.8; 15.1)	<0.001
Cortisol T90 (mcg/dL)	12.8 (8.5; 15.5)	16.8 (13.7; 19.0)	9.8 (5.7; 12.6)	<0.001
Cortisol T120 (mcg/dL)	10.0 (6.6; 13.0)	12.9 (11.0; 15.4)	8.3 (5.1; 10.1)	<0.001

MED (IQR): Median (Interquartile Range)

may result in a higher detection rate of chronic adrenal insufficiency due to long-term glucocorticoid therapy in women compared to men. However, there was no statistically significant difference in gender between the groups with and without adrenal insufficiency in our study (Table 2). Most patients had underlying conditions typically managed within internal medicine subspecialties, including musculoskeletal, otolaryngologic, and endocrine conditions (Table 1). Clinical manifestations related to glucocorticoid-associated adverse effects were infrequent among patients in our study (Table 1). This can be attributed to the fact that participants were sampled during the maintenance phase, when low-dose glucocorticoid therapy was being administered and the underlying disease was already well controlled. At this stage, the impact of exogenous glucocorticoids on the body is likely minimal. Consequently, this is also the point at which clinicians typically consider discontinuing glucocorticoid therapy, prompting the need for adrenal function assessment to ensure safe withdrawal. When comparing the comorbidities between two groups, in the adrenal insufficiency group, the proportion of patients with comorbidities was higher compared to the non-adrenal insufficiency group, but this difference was not statistically significant (Table 3). However, a study by Tran Quang Nam et al., reported that most of comorbidities are statistically significantly higher in the adrenal insufficiency group compared to the non-adrenal insufficiency group.[7] The lack of statistically significant differences in comorbidities between the two groups may be due to a smaller sample size, which reduces the power of the study to detect significant differences between groups. Although the total sample size was 96 patients, dividing them into two groups reduced the sample size of each group, diminishing the ability to detect statistically significant differences. To address this, increasing the sample size could enhance accuracy and the ability to detect statistically significant differences between the group.

All patients were prescribed glucocorticoid therapy, predominantly prednisolone and methylprednisolone. The cumulative duration of glucocorticoid treatment in the adrenal insufficiency group was 12 months, which was significantly longer compared to 3 months in the non-adrenal insufficiency group (Table 2). Our findings are consistent with the 2024 Clinical Practice Guidelines jointly issued by the European Society of Endocrinology and the Endocrine Society, which state that among the risk factors contributing to the development of adrenal insufficiency, a duration of glucocorticoid therapy ranging from 1 to 3 months is associated with a moderate risk, whereas treatment exceeding 3 months is associated with a high risk of adrenal insufficiency.[6] The observed association is biologically plausible, as prolonged exposure to exogenous glucocorticoids leads to sustained suppression of the hypothalamic-pituitary-adrenal (HPA) axis, impairing the body's endogenous cortisol production. This prolonged suppression contributes to the pathophysiology underlying secondary adrenal insufficiency.

All patients underwent the insulin tolerance test (ITT), during which we observed that serum cortisol levels at all time points were significantly lower in the adrenal insufficiency group compared to the non-adrenal insufficiency group (Table 3). Currently, there is a global trend toward recommending the replacement of dynamic stimulation tests with simpler, more affordable, and widely accessible static measurements that maintain comparable diagnostic efficacy. In this light, we further investigated the correlation between baseline cortisol levels and peak cortisol levels following the ITT. We found a moderately strong positive correlation between these two parameters ($r = 0.62$, $p < 0.001$) (Figure 1). Our findings are consistent with previous studies. Eturk et al. reported a significant correlation between morning cortisol and peak cortisol after hypoglycemia ($r = 0.63$), as did Hagg et al., ($r = 0.73$) and Tran Quang Nam et al. ($r = 0.8$).[7-9] A moderate-to-strong positive correlation indicating that as baseline cortisol level increased, peak cortisol level from ITT tended to increase correspondingly. This finding suggests a statistically and clinically meaningful association between the two parameters. Given the strength of the observed correlation, it is reasonable to hypothesize that baseline cortisol level may serve as an important clinical indicator for predicting changes in peak cortisol level from ITT. This potential association could have practical implications for screening, risk stratification, and disease monitoring in clinical practice.

In addition, ROC curve analysis of morning baseline serum cortisol for diagnosing adrenal insufficiency yielded an area under the curve (AUC) of 0.83 (95% CI: 0.78–0.89; $p < 0.05$). Our findings are consistent with those of Tran Quang Nam, who reported an AUC of 0.71 (95% CI: 0.6–0.8; $p < 0.0005$).[7] Similarly, Ashley et al., demonstrated good diagnostic performance of baseline cortisol, with an AUC of 0.81 (95% CI: 0.77–0.84).[10] Given the range of AUC values reported across the aforementioned studies, morning serum cortisol demonstrates good discriminative ability

in differentiating between individuals with and without adrenal insufficiency. Therefore, it may serve as a reliable alternative to dynamic testing in the evaluation of adrenal function.

Based on the sensitivity and specificity at different cut-off points in Table 6, we constructed a ROC curve to illustrate the diagnostic value of morning serum cortisol for adrenal insufficiency in Figure 2. At the same time, the optimal cut-off value of morning serum cortisol was determined using the Youden Index, as shown in the Table 7. When different baseline cortisol cut-off values were applied, notable variations in diagnostic performance were observed. At a cut-off of 8 μg/dL, sensitivity was relatively low (59%), which increases the false negatives (41%), although specificity remained acceptable (76%). By contrast, cut-offs of 10 μg/dL and 11 μg/dL yielded substantially higher sensitivities (78% and 82%, respectively), thereby reducing the false negatives. However, this improvement in sensitivity was offset by a marked decline in specificity (57% and 49%, respectively), resulting in a greater number of false positives. From a clinical perspective, lower cut-offs such as 8 μg/dL may provide greater diagnostic confidence for confirming adrenal insufficiency, whereas higher cut-offs (10–11 μg/dL) are more suitable for excluding the disease, where sensitivity is prioritized over specificity. These findings highlight the importance of selecting cut-off thresholds based on the clinical context and the relative balance between minimizing false negatives versus false positives. If the optimal cut-off value for morning serum cortisol is set at 9.0 μg/dL, the test demonstrates a sensitivity of 69% and a specificity of 67%. This means that the test can correctly identify 69% of patients with true adrenal insufficiency, but 31% of true cases may go undetected, which could lead to premature discontinuation of glucocorticoid therapy by the treating physician without proper monitoring. These patients are at risk of acute adrenal insufficiency during periods of acute stress. On the other hand, the test identifies 67% of patients without adrenal insufficiency, meaning 33% of patients who actually have normal adrenal function may be misdiagnosed and continue unnecessary glucocorticoid therapy (Table 7). When compared to other studies, we found that Hagg et al., reported a morning serum cortisol cutoff of 10.9 μg/dL, which yielded a sensitivity of 67% and a specificity of 94%.[8] Eturk et al., found that at a morning serum cortisol cutoff of 10 μg/dL, the sensitivity was 62% and the specificity was 77%.[7] Tran Quang Nam et al., observed that at a cutoff of 9.9 μg/dL, the sensitivity was 64% and the specificity was 72%.[9] Furthermore, we observed that the morning serum cortisol cutoff of 3 μg/dL had a positive predictive value (PPV) of 100%, meaning that when morning serum

Table 6. The diagnostic value of cortisol

Cortisol cutoff	Sen	Spe	PPV	NPV
3	0.01 (0.00 - 0.04)	1.00 (0.96 - 1.00)	1.00 (0.03 - 1.00)	0.41 (0.35 - 0.48)
4	0.11 (0.06 - 0.17)	0.98 (0.92 - 1.00)	0.88 (0.62 - 0.98)	0.43 (0.36 - 0.50)
5	0.21 (0.15 - 0.29)	0.95 (0.88 - 0.98)	0.85 (0.68 - 0.95)	0.46 (0.38 - 0.53)
6	0.37 (0.29 - 0.46)	0.91 (0.83 - 0.96)	0.86 (0.74 - 0.94)	0.50 (0.42 - 0.58)
7	0.48 (0.39 - 0.57)	0.84 (0.74 - 0.90)	0.81 (0.70 - 0.89)	0.53 (0.44 - 0.61)
8	0.59 (0.50 - 0.67)	0.76 (0.66 - 0.84)	0.78 (0.68 - 0.86)	0.56 (0.47 - 0.65)
9	0.69 (0.61 - 0.77)	0.67 (0.56 - 0.77)	0.75 (0.67 - 0.83)	0.60 (0.50 - 0.70)
10	0.78 (0.70 - 0.85)	0.57 (0.46 - 0.67)	0.72 (0.64 - 0.80)	0.64 (0.53 - 0.75)
11	0.82 (0.74 - 0.88)	0.49 (0.39 - 0.60)	0.70 (0.62 - 0.77)	0.65 (0.53 - 0.76)
12	0.89 (0.83 - 0.94)	0.38 (0.28 - 0.49)	0.68 (0.60 - 0.75)	0.71 (0.57 - 0.83)
13	0.92 (0.85 - 0.96)	0.29 (0.20 - 0.39)	0.65 (0.58 - 0.72)	0.70 (0.53 - 0.84)
14	0.99 (0.96 - 1.00)	0.18 (0.10 - 0.27)	0.63 (0.56 - 0.70)	0.94 (0.71 - 1.00)
15	1.00 (0.97 - 1.00)	0.08 (0.03 - 0.15)	0.61 (0.54 - 0.67)	1.00 (0.59 - 1.00)

Sens: Sensitivity; Spec: Specificity; PPV: Positive Predicted Value; NPV: Negative Predicted Value

Table 7. The diagnostic performance of the optimal cortisol cutoff value determined by Youden's index

	Value
Optimal cortisol cutoff value (μg/dL)	9.0
Sensitivity (%)	69 (61-77)
Specificity (%)	67 (56-77)
Positive predicted value	75 (67-83)
Negative predicted value	60 (50-70)

Table 8. Multivariate logistic regression analysis for predictors of adrenal insufficiency

Model	N	Variable	Model 1	Model 2	Model 3	Model 4
Intercept			-0.61 (-2.57; 1.29)	-1.02 (-1.81; -0.30)	1.60 (0.09; 3.23)	2.80 (1.51; 4.29)
Age (per 10-year increase)	96	0.13 (-0.16; 0.42)	-0.11 (-0.52; 0.29)			
Male sex	96	-0.68 (-1.66; 0.28)	-0.09 (-1.27; 1.07)			
Dyslipidemia	96	0.90 (0.05; 1.80)	0.57 (-0.70; 1.88)			
Hypertension	96	0.88 (-0.04; 1.87)	0.85 (-0.60; 2.32)	1.12 (0.08; 2.24)	1.77 (0.52; 3.19)	
Osteoporosis	96	0.85 (-0.22; 2.05)	0.07 (-1.42; 1.57)			
Total duration of glucocorticoid treatment (months)	96	0.08 (0.04; 0.14)	0.08 (0.03; 0.14)	0.08 (0.04; 0.14)	0.10 (0.04; 0.17)	
Abdominal obesity	96	0.90 (-0.09; 2.01)	0.10 (-1.30; 1.48)			
Moon face	96	17.40 (-88.63; NA)	16.82 (-58.33;NA)	16.96 (-72.83; NA)	17.83 (-87.49; NA)	
Cataracts	96	1.72 (-0.07; 4.67)	0.50 (-1.94; 3.72)			
Baseline cortisol levels (μg/dL)	96	-0.28 (-0.44; -0.14)			-0.33 (-0.52;-0.16)	-0.28 (-0.44; -0.14)
AUC (KTC 95%)			0.81 (0.73; 0.90)	0.81 (0.72; 0.90)	0.87 (0.80; 0.94)	0.75 (0.65; 0.85)

cortisol levels are below 3 μg/dL, it can accurately detect 100% of patients with glucocorticoid-induced adrenal insufficiency. In contrast, the morning serum cortisol cutoff of 15 μg/dL had a negative predictive value (NPV) of 100%, indicating that cortisol levels above 15 μg/dL can reliably identify 100% of patients with normal adrenal function (Table 6).Therefore, using morning serum cortisol alone may not be sufficiently reliable for determining adrenal function, as it could result in misdiagnosis in certain cases.

Based on the analyses presented, we found that morning serum cortisol demonstrates a reasonable capacity for distinguishing between adrenal insufficiency and normal adrenal function. However, it cannot be considered an ideal test to fully replace dynamic testing. Therefore, we propose that, to enhance the diagnostic value of morning serum cortisol, it should not be employed in isolation for the assessment of adrenal function. Instead, it should be used in conjunction with clinical characteristics of the study population to improve the diagnostic accuracy for adrenal insufficiency. When comparing diagnostic models, we found that Model 4, which relied solely on the morning serum cortisol test, demonstrated a reasonable diagnostic performance with an AUC of 0.75. In contrast, Model 2, which included only the clinical characteristics of the study population, achieved an AUC of 0.81. This further emphasizes the critical role of taking a thorough medical history, considering patient comorbidities, and conducting clinical examinations, highlighting that the morning serum cortisol test alone should not be solely relied upon for diagnosing adrenal insufficiency. Model 3, which incorporated both the clinical characteristics of the study population such as Cushingoid appearance, duration of glucocorticoid therapy, history of hypertension and morning serum cortisol levels, demonstrated the highest diagnostic performance for adrenal insufficiency, with an AUC of 0.87. This finding underscores the enhanced diagnostic value derived from integrating clinical characteristics with biochemical markers, thus providing the most accurate assessment of adrenal insufficiency. Based on the models outlined above, we conclude that in clinical practice, when approaching a patient with stable underlying disease who has been tapered to a daily dose of ≥5 mg of prednisone (or an equivalent dose of another glucocorticoid), and is under consideration for adrenal function assessment, it is crucial to gather baseline characteristics such as Cushingoid appearance, duration of glucocorticoid therapy, history of hypertension and perform a morning serum cortisol test. The combination of these factors offers superior diagnostic value for adrenal insufficiency, with an AUC of 0.87, enabling the clinician to make informed decisions regarding the continuation or safe discontinuation of glucocorticoid therapy. Another notable point, according to the guidelines by Hosmer and Lemeshow, models with an AUC ranging from 0.9 to 1.0 demonstrate excellent discriminative ability between disease and non-disease cases.[11] Our combined model, with an AUC of 0.87, approaches the threshold for excellent diagnostic performance, suggesting that it may serve as a potential alternative to insulin tolerance test for assessing adrenal function - particularly in healthcare settings where such testing is not feasible, such as in Vietnam.

CONCLUSION

After the ITT, we determined that the prevalence of adrenal insufficiency was 58.3%, while the non-adrenal insufficiency group accounted for 41.7%. The morning serum cortisol test demonstrated a diagnostic performance with an AUC of 0.83 (95% CI: 0.78–0.89), indicating its strong ability to distinguish between adrenal insufficiency and normal adrenal function. If the optimal cutoff value for morning serum cortisol is set at 9.0 μg/dL, the test demonstrates a sensitivity of 69% and a specificity of 67%. Besides, we observed that the morning serum cortisol cutoff of 3 μg/dL had a positive predictive value (PPV) of 100% and the morning serum cortisol cutoff of 15 μg/dL had a negative predictive value (NPV) of 100%. Model 3, which integrates clinical characteristics such as Cushingoid appearance, duration of glucocorticoid therapy, history of hypertension with morning cortisol levels, exhibited the highest diagnostic accuracy with an AUC of 0.87 and may serve as a reliable alternative to the insulin tolerance test for adrenal insufficiency assessment. In settings where dynamic testing is not feasible due to cost, complexity, or lack of experience, we recommend implementing Model 3 as a practical and cost-effective approach for adrenal function evaluation, as it requires only a single blood sample and is widely accessible.

This study has several strengths, including the integration of key clinical characteristics with baseline cortisol level, which significantly improved diagnostic accuracy and provided a cost-effective, accessible alternative to insulin tolerance test. The insulin tolerance test, as our reference standard, strengthened the validity of our findings, while the identification of clinically relevant cortisol thresholds (<3 μg/dL and >15 μg/dL) offers immediate applicability in practice. However, certain limitations should be acknowledged. The single-center, cross sectional design with a modest sample size may limit generalizability. In addition, the predictive model was not externally validated, and further studies are required to confirm its utility across diverse healthcare settings. Nevertheless, our findings support the use of baseline cortisol combined with key clinical characteristics as a practical approach for assessing adrenal function, particularly in settings where dynamic testing is not feasible, such as in Vietnam.

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Statement of Authorship
All authors certified fulfillment of ICMJE authorship criteria.

CRediT Author Statement
DTN: Conceptualization, Methodology, Validation, Writing – original draft preparation, Writing – review and editing, Data curation; **TTN:** Formal Analysis, Methodology, Writing – review and editing; **KQT:** Conceptualization, Writing – review and editing, Supervision.

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