

The impact of prolonged high-concentration cortisol exposure on cognitive function and risk factors: Evidence from Cushing's disease patients

Journal of Alzheimer's
Disease Reports
Volume 9: 1–8
© The Author(s) 2025
Article reuse guidelines:
sagepub.com/journals-permissions
DOI: 10.1177/25424823251338161
journals.sagepub.com/home/alr



Yuxiang Sun^{1,2,#} , Junpeng Xu^{2,#}, Xiaoque Zheng^{2,#}, Chunhui Li¹, Dongsheng Kong², Qijia Wu², Zihao Zhu¹, Shiyu Feng² and Yanyang Zhang²

Abstract

Background: Prolonged high-concentration cortisol exposure may impair cognitive function, but its mechanisms and risk factors remain unclear in humans.

Objective: Using Cushing's disease patients as a model, this study explores these effects and develops a predictive model to aid in managing high-risk patients.

Methods: This single-center retrospective study included 107 Cushing's disease patients (January 2020–January 2024) at the First Medical Center of the PLA General Hospital. Cognitive function, assessed using the Montreal Cognitive Assessment, revealed 58 patients with cognitive impairment and 49 with normal cognitive function. Patients were divided into training (n = 53) and validation cohorts (n = 54) for constructing and validating the predictive model. Risk factors were identified via univariate analysis and least absolute shrinkage and selection operator regression, and a nomogram prediction model was developed. Performance was evaluated using receiver operating characteristic (ROC) curves, calibration curves, and decision curve analysis (DCA).

Results: Cortisol AM/PM ratio, 8 a.m. cortisol concentration, body mass index, and fasting plasma glucose were significant risk factors for cognitive impairment. The nomogram demonstrated strong predictive ability, with ROC values of 0.80 (training) and 0.91 (validation). DCA indicated superior clinical utility compared to treating all or no patients.

Conclusions: This study confirms the significant impact of prolonged high cortisol exposure on cognitive function and identifies key risk factors. The nomogram model offers robust performance, providing a valuable tool for managing Cushing's disease patients' cognitive health and informing strategies for other cortisol-related disorders.

Keywords

Alzheimer's disease, cognitive function, Cushing's disease, predictive model, prolonged high-concentration cortisol exposure

Received: 27 December 2024; accepted: 12 April 2025

Introduction

Chronic stress and prolonged pressure increasingly pose significant burdens on individual health and social systems, particularly on a global scale. Their impact on cognitive function, mental health, and physical well-being cannot be ignored.¹ Long-term stress responses and sustained exposure to pressure not only elevate the risk of multiple diseases but also result in considerable socioeconomic burdens. According to the World Health Organization (WHO), approximately 300 million people worldwide suffer from depression, with stress and emotional disorders being critical contributing factors.² This

¹Department of Neurosurgery, Affiliated Hospital of Hebei University, Baoding, China

²Department of Neurosurgery, the First Medical Center of Chinese PLA General Hospital, Beijing, China

[#]These authors have contributed equally to this work

Corresponding authors:

Shiyu Feng, Department of Neurosurgery, the First Medical Center of Chinese PLA General Hospital, No. 28, FuXing Road, Beijing, China.
Email: fengshiyu72123@163.com

Yanyang Zhang, Department of Neurosurgery, the First Medical Center of Chinese PLA General Hospital, No.28, FuXing Road, Beijing, China.
Email: sjwkzyy@163.com



Creative Commons Non Commercial CC BY-NC: This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 License (<https://creativecommons.org/licenses/by-nc/4.0/>) which permits non-commercial use, reproduction and distribution of the work without further permission provided the original work is attributed as specified on the SAGE and Open Access page (<https://us.sagepub.com/en-us/nam/open-access-at-sage>).

phenomenon may be associated with prolonged exposure to high concentrations of cortisol induced by chronic stress.³ Such long-term elevated cortisol exposure is thought to exert adverse effects on multiple systems, including the nervous system, leading to anxiety, depression, and cognitive impairment. While the roles of anxiety and depression have been well established,⁴ the specific impact on cognitive function remains unclear.

Research suggests that abnormally elevated cortisol levels significantly affect brain structure and function. The hippocampus, a key target highly sensitive to cortisol and central to learning and memory, is particularly affected. High cortisol exerts its effects through glucocorticoid receptors and mineralocorticoid receptors in the hippocampus, mediating neurophysiological responses. Prolonged activation may lead to neuronal damage, reduced neuroplasticity, and cognitive impairment.^{5,6} Additionally, brain regions such as the prefrontal cortex and amygdala are also impacted, potentially causing attentional deficits, impaired executive function, and emotional regulation disturbances.⁷ Furthermore, abnormal diurnal cortisol rhythms are closely linked to neuroinflammation, oxidative stress, and cerebrovascular lesions.^{8,9} These mechanisms may interact synergistically to exacerbate cognitive impairment. While animal studies provide substantial evidence for cortisol's effects on cognitive function, human studies face ethical constraints and experimental limitations. The lack of models for long-term stress and pressure in humans, coupled with challenges in conducting long-term follow-ups, highlights the need for suitable research subjects.

Cushing's disease is an endocrine disorder caused by excess adrenocorticotrophic hormone (ACTH) secretion by anterior pituitary adenomas, leading to abnormally elevated cortisol levels.¹⁰ The unique pathological features of Cushing's disease offer a natural model for studying the effects of prolonged high cortisol exposure on human cognitive function. Patients with Cushing's disease often experience cognitive impairments, with clinical manifestations including memory decline, attention deficits, and impaired executive function.^{11–13} However, the specific mechanisms and risk factors underlying these impairments remain unclear.

Against this backdrop, this study uses Cushing's disease patients as subjects to systematically evaluate the impact of prolonged high cortisol exposure on cognitive function and analyze associated risk factors. Additionally, we develop a nomogram prediction model aimed at improving the identification of high-risk patients, providing a reference for clinical interventions, and offering new perspectives and evidence for the cognitive management and research of cortisol-related disorders.

Methods

Study subjects

This study is a single-center retrospective study that included 107 patients diagnosed with Cushing's disease at

the First Medical Center of the PLA General Hospital between January 2017 and January 2024. Inclusion criteria were as follows: (i) meeting the WHO diagnostic criteria for Cushing's disease; (ii) disease duration >3 months; (iii) no prior surgical treatment; (iv) complete laboratory and imaging data; (v) no other neurological or psychiatric disorders that could cause cognitive impairment (e.g., dementia, depression, stroke). Exclusion criteria included: (i) disease duration <3 months; (ii) prior surgical treatment; (iii) missing critical baseline or laboratory data; (iv) severe visual or hearing impairments that could affect cognitive testing results. A total of 107 patients were included in the study, among whom 58 had cognitive impairment and 49 exhibited mild cognitive decline. Cognitive function was classified as follows: Montreal Cognitive Assessment (MoCA) score ≤ 26 was defined as cognitive impairment, 27–29 as mild cognitive decline, and 30 as normal cognitive function.

Study design

A random allocation method was used to divide all patients into a training cohort ($n = 53$) and a validation cohort ($n = 54$) at a 5:5 ratio. The training cohort was used for variable selection and predictive model development, while the validation cohort was used for performance evaluation of the model. The study was approved by the hospital ethics committee (approval number: [S2021-677-01]).

Clinical data collection

Clinical characteristics and laboratory data of patients were obtained from the hospital's electronic medical record system and included the following: (i) Demographic and clinical characteristics: age, sex, disease duration, years of education, body mass index (BMI), systolic blood pressure, and diastolic blood pressure; (ii) Laboratory indicators: fasting plasma glucose (FPG), 24-h urinary free cortisol, serum cortisol concentrations (0 a.m., 8 a.m., 4 p.m.), ACTH concentrations (0 a.m., 8 a.m., 4 p.m.), total cholesterol, triglycerides, alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transferase, cortisol AM/PM ratio (CORT AM/PM), and results of low-dose dexamethasone suppression tests and high-dose dexamethasone suppression tests; (iii) Cognitive function assessment: conducted using the MoCA scale.

Statistical analysis and model development

Categorical variables were expressed as numbers (%), and continuous variables as mean $\pm$ standard deviation (SD) or median (interquartile range, IQR). Intergroup comparisons

were performed using the chi-square test or Fisher's exact test for categorical variables. A nomogram was constructed to predict the risk factors for cognitive impairment in patients exposed to prolonged high cortisol levels. Significant clinical features associated with cognitive function were identified through univariate analysis and least absolute shrinkage and selection operator (LASSO) regression analysis.

Based on the final results, a novel nomogram was developed, incorporating all independent prognostic factors to predict the presence or absence of cognitive impairment in individuals exposed to prolonged high cortisol levels. The performance of the nomogram was evaluated using the concordance index (C-index), area under the receiver operating characteristic (ROC) curve (AUC), calibration curves, and decision curve analysis (DCA). The C-index was calculated using 1,000 bootstrap samples to assess the internal validity of the model. Each patient's total score was calculated using the nomogram approach.

Statistical analysis was performed using R programming language and version 4.2.3 of the R environment (<http://cran.r-project.org>). The main R packages used in this study included gtsummary (version 1.7.0), survival (version 3.5-3), RMS (version 6.3-0), time ROC (version 0.4), and ggplot2 (version 3.4.0).

Results

Patient characteristics

A total of 107 patients with Cushing's disease were included in this study. MoCA scores revealed that all patients exhibited either cognitive decline or impairment. Among them, 58 patients (54.2%) were classified into the cognitive impairment group, and 49 patients (45.8%) were categorized into the cognitive decline group. Significant differences were observed in demographic characteristics and clinical indicators between the two groups. Detailed information is presented in Table 1.

Model development

In the modeling cohort, LASSO regression analysis was used for variable selection. The regression coefficient path diagram and cross-validation curve are shown in Figure 1A and 1B. To ensure a good model fit, the λ corresponding to the minimum mean squared error was chosen through cross-validation. Four variables were identified through LASSO regression analysis: CORT AM/PM, COR-8am, FPG, and BMI. These variables were ultimately deemed risk factors for cognitive impairment associated with prolonged high cortisol exposure. Based on these four significant variables, a nomogram was developed to predict cognitive impairment under prolonged high cortisol exposure, and the model was visualized using a nomogram (Figure 2).

Model performance and validation

To comprehensively evaluate the model's performance, multiple metrics were employed to verify its accuracy, stability, and clinical utility, including the concordance index (C-index), AUC, calibration curves, and DCA. The AUC values for the training cohort (Figure 3A) and the internal validation cohort (Figure 3B) were 0.80 and 0.91, respectively. These results indicate that the nomogram model effectively distinguishes patients with cognitive impairment in different sample datasets and demonstrates strong predictive accuracy. Calibration curves showed a high level of agreement between the predicted and actual probabilities of cognitive impairment in both the training cohort (Figure 4A) and the validation cohort (Figure 4B), further confirming the model's stability and utility.

To assess the clinical utility of the model, DCA was performed (Figure 5). The results demonstrated that the clinical benefit of using the model to predict cognitive impairment was significantly higher than strategies of treating all patients or treating none (Figure 5). This finding suggests that the nomogram model provides substantial net benefit in clinical decision-making, effectively aiding clinicians in identifying high-risk patients and implementing appropriate interventions.

Discussion

This study used patients with Cushing's disease as a model to investigate the effects of prolonged high-concentration cortisol exposure on human cognitive function. The findings revealed that individuals exposed to long-term high cortisol levels generally experienced cognitive decline, with the CORT AM/PM, COR-8am, BMI, and FPG identified as major risk factors for cognitive impairment. Additionally, the developed nomogram model demonstrated excellent predictive performance in both the training (AUC = 0.80) and validation (AUC = 0.91) cohorts, highlighting its strong discriminative ability and clinical utility. These findings provide a foundation for mechanistic research and clinical management of prolonged high cortisol exposure.

BMI, FPG, CORT AM/PM, and COR-8am, as risk factors, are closely related to cortisol levels and its effects on the nervous system. Increased BMI was identified as an independent risk factor for cognitive impairment, likely due to chronic inflammation and oxidative stress caused by metabolic disorders.¹⁴⁻¹⁶ Obesity and elevated cortisol levels may form a vicious cycle, further exacerbating damage to the nervous system. Studies have shown that reduced cerebral blood flow and neuronal damage in obese individuals are directly linked to cognitive impairment,¹⁷ underscoring the importance of monitoring metabolic status in Cushing's disease patients. High blood glucose was another critical risk factor, potentially affecting cognitive function through various mechanisms:

Table 1. General characteristics of patients.

Variables	Total (n = 107)	0 (n = 49)	1 (n = 58)	P
sex, n (%)				
1	10 (9)	5 (10)	5 (9)	1
2	97 (91)	44 (90)	53 (91)	
age, Mean $\pm$ SD	41.22 $\pm$ 11.19	39.16 $\pm$ 11.21	42.97 $\pm$ 10.96	0.08
Education y, Median (Q1,Q3)	12 (8, 16)	12 (8, 16)	12 (8.25, 15)	0.835
BMI, Mean $\pm$ SD	27.01 $\pm$ 3.46	25.49 $\pm$ 2.25	28.29 $\pm$ 3.79	<0.001
Illness duration, Median (Q1,Q3)	26 (12, 48)	24 (12, 48)	33 (12, 48)	0.6
COR-0am, Mean $\pm$ SD	565.86 $\pm$ 207.53	513.69 $\pm$ 185.87	609.94 $\pm$ 216.06	0.015
COR-8am, Mean $\pm$ SD	725.63 $\pm$ 259.03	612.26 $\pm$ 197.79	821.41 $\pm$ 267.29	<0.001
COR-4pm, Median (Q1,Q3)	619.19 (491.14, 744.17)	598.3 (472.49, 678.18)	650.43 (503.34, 803.88)	0.109
ACTH0am, Median (Q1,Q3)	12.4 (9.02, 18.4)	11 (8.46, 17.2)	13.95 (9.57, 19.51)	0.114
ACTH8am, Median (Q1,Q3)	15.2 (11.1, 23.5)	13.3 (10.6, 19.4)	17.4 (13.33, 26.27)	0.027
ACTH4pm, Median (Q1,Q3)	15.9 (10.45, 22.75)	13.6 (10.4, 22.6)	16.6 (10.95, 25.15)	0.275
UFC, Median (Q1,Q3)	1644.9 (1146.2, 2501.75)	1483 (1092.3, 2020.6)	1931 (1168.85, 2793.02)	0.131
LDDST-ACTH, Median (Q1,Q3)	16.9 (9.31, 21.15)	16.1 (8.35, 20.6)	17.25 (10.12, 21.17)	0.555
LDDST-CORT, Median (Q1,Q3)	532.95 (390.46, 787.61)	501.63 (360.4, 792.18)	568.37 (398.76, 781.7)	0.606
LDDST-UFC, Median (Q1,Q3)	1050.8 (531.9, 2077.2)	880.6 (454.4, 2419.9)	1200 (580.62, 2010.23)	0.589
HDDST-ACTH, Median (Q1,Q3)	8.81 (5.2, 15.7)	8.48 (4.91, 16.6)	9.12 (5.42, 14.45)	0.837
HDDST-CORT, Median (Q1,Q3)	222.3 (62.41, 354.31)	222.3 (61.7, 348.84)	217.56 (76.25, 356.78)	0.662
HDDST-UFC, Median (Q1,Q3)	336.9 (130.9, 870.86)	281.2 (128.4, 791.7)	391.4 (140.25, 923.43)	0.488
SBP, Mean $\pm$ SD	159.09 $\pm$ 26.08	157.76 $\pm$ 26.67	160.22 $\pm$ 25.75	0.629
DBP, Median (Q1,Q3)	105 (92, 116.5)	105 (90, 119)	102.5 (94.5, 114)	0.927
TC, Median (Q1,Q3)	5.13 (4.46, 6.17)	4.92 (4.47, 5.72)	5.24 (4.44, 6.31)	0.386
TG, Median (Q1,Q3)	1.42 (0.99, 2.04)	1.39 (0.99, 2.41)	1.42 (0.99, 1.97)	0.861
ALT, Median (Q1,Q3)	23 (17.55, 33.7)	20.7 (15.8, 33)	23.85 (18.45, 34.3)	0.35
AST, Median (Q1,Q3)	15.2 (13, 18.5)	14.1 (12.7, 18.5)	16.35 (13.62, 18.45)	0.184
GGT, Median (Q1,Q3)	27.6 (21.75, 44.25)	26.7 (22.6, 45.9)	28.95 (21.32, 41.9)	0.913
FPG, Median (Q1,Q3)	7.62 (5.43, 9.66)	5.7 (4.83, 7.49)	8.95 (7.05, 10)	<0.001
CORT AM/PM, Median (Q1,Q3)	1.19 (0.99, 1.34)	1.05 (0.88, 1.2)	1.25 (1.15, 1.4)	<0.001

ACTH: adrenocorticotrophic hormone; ALT: alanine aminotransferase; AST: aspartate aminotransferase; BMI, body mass index; COR/CORT: cortisol; DBP: diastolic blood pressure; FPG: fasting plasma glucose; GGT: gamma-glutamyl transferase; HDDST: high-dose dexamethasone suppression tests; LDDST: low-dose dexamethasone suppression tests; SBP: systolic blood pressure; TC: total cholesterol; TG: triglycerides; UFC: urinary free cortisol.

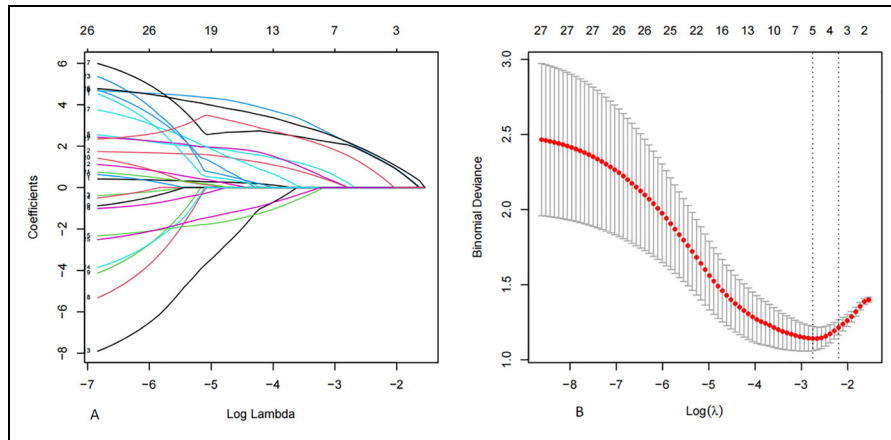


Figure 1. LASSO Cox regression model construction. (A) LASSO coefficient of 27 features. (B) Selection of tuning parameter (k) for the LASSO model.

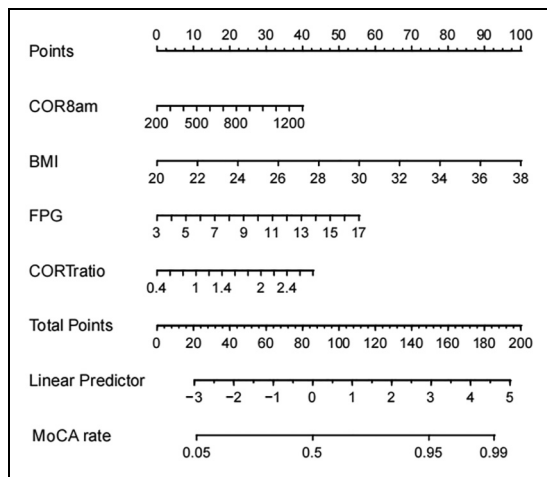


Figure 2. Nomogram predicting cognitive impairment in patients with prolonged high cortisol exposure.

prolonged hyperglycemia can lead to cerebrovascular damage and impaired blood supply to the brain;¹⁸ it may also directly harm neurons through oxidative stress and inflammatory responses.¹⁹ Moreover, chronic hyperglycemia alters insulin signaling pathways, disrupting glucose metabolism in the brain and further aggravating cognitive decline.²⁰ Additionally, the study showed that disrupted cortisol circadian rhythms (elevated CORT AM/PM) and increased morning cortisol peaks (COR-8am) were closely associated with cognitive impairment. Circadian rhythm disruption may accelerate hippocampal atrophy and prefrontal cortex dysfunction by affecting the regulation of the hypothalamic-pituitary-adrenal (HPA) axis.²¹ Excessive morning cortisol peaks may exacerbate neuroinflammation and synaptic dysfunction,²² a finding also supported by previous animal studies.

Cushing's disease serves as an effective model for studying high cortisol states induced by chronic stress, given the high similarity in pathophysiological mechanisms between the

two. Cushing's disease results from tumor-induced HPA axis hyperactivation, causing sustained cortisol overproduction,²³ while chronic stress similarly activates the HPA axis, maintaining cortisol at persistently high levels. Although the etiology of Cushing's disease is endogenous and pathological, whereas high cortisol in chronic stress is environmentally induced, both share similar features such as metabolic disturbances (e.g., insulin resistance, central obesity), immunosuppression (e.g., increased infection susceptibility), osteoporosis, and psychological disorders (e.g., anxiety and depression).²⁴ Therefore, Cushing's disease provides an effective model for studying metabolic, immune, and neurological changes in high cortisol states, offering experimental evidence for understanding chronic stress-related disorders and developing intervention strategies.

The results of this study align with previous animal experiments. For instance, animal studies have shown that prolonged cortisol exposure leads to hippocampal atrophy and neuronal damage, impairing cognitive function.²⁵ This study provides supportive evidence in human samples. Furthermore, prior research has found that disrupted cortisol circadian rhythms are often associated with executive function decline in patients with depression,²⁶ consistent with our findings that CORT AM/PM is significantly associated with cognitive impairment in Cushing's disease patients. Unlike earlier studies focusing primarily on cortisol's direct neurotoxic effects, this study integrated metabolic indicators (e.g., BMI, FPG) to comprehensively analyze the interaction between cortisol and metabolic disturbances, expanding the understanding of mechanisms underlying cortisol-induced cognitive impairment.

Moreover, unlike previous research that was predominantly based on animal models, this study systematically analyzed data from 107 Cushing's disease patients, further validating these mechanisms in humans. The construction of the nomogram model significantly enhanced predictive accuracy, providing a practical tool for clinical application.

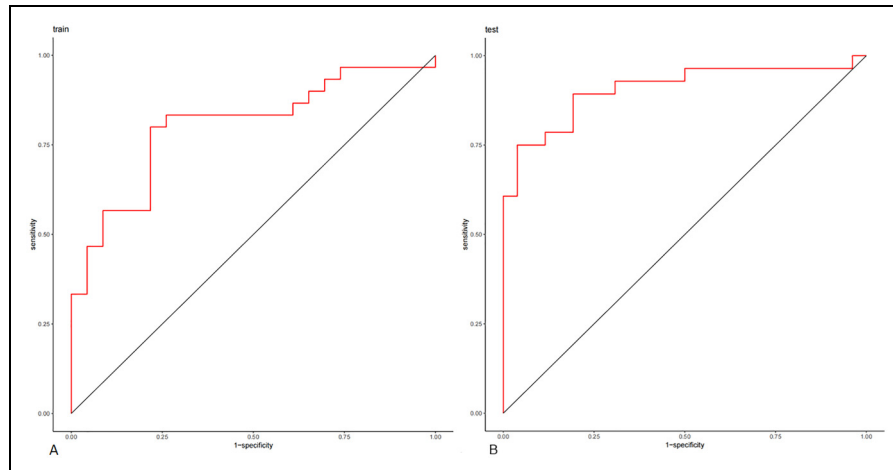


Figure 3. The ROC curve of the predictive model for cognitive impairment in patients with prolonged high cortisol exposure. (A) Derivation cohort. (B) Validation cohort.

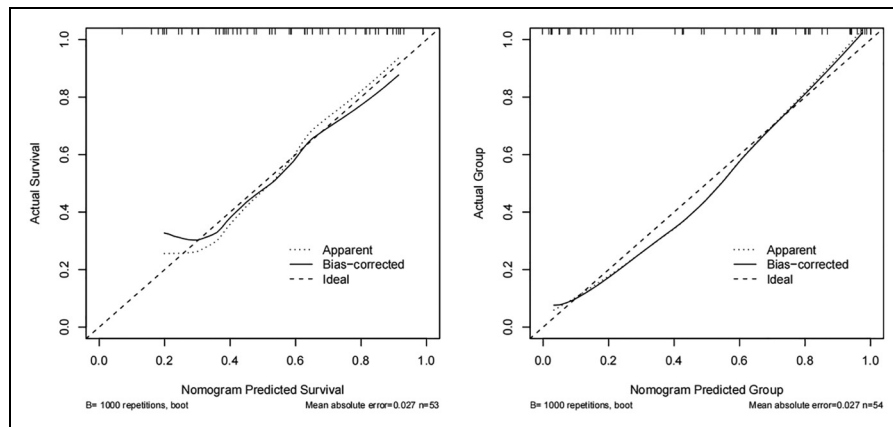


Figure 4. Calibration curves of the nomogram. (A) Derivation cohort. (B) Validation cohort.

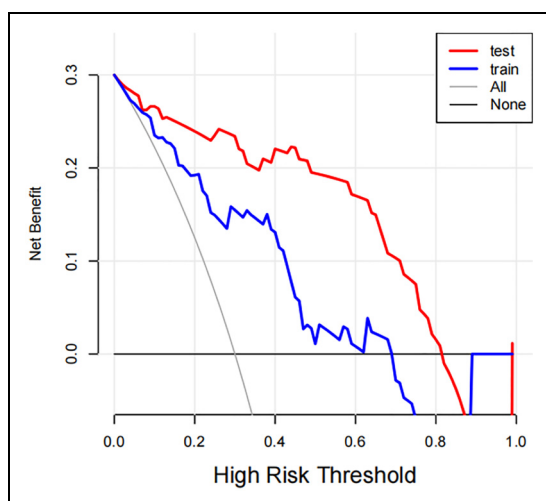


Figure 5. DCA curves of the nomogram in the training cohort and test cohort.

Despite providing important evidence for the impact of prolonged high cortisol exposure on cognitive function, this study has limitations. First, as a single-center retrospective study with a limited sample size, the results may lack generalizability and require prospective validation. Although Cushing's disease serves as a model for high cortisol exposure, further validation in populations experiencing chronic stress or prolonged pressure is needed. Second, the lack of long-term follow-up data prevents evaluation of the effects of surgical treatment or other interventions on cognitive function. Third, this study did not consider the impact of sex hormones on cortisol levels and cognitive function. Sex hormones (such as estrogen and testosterone) may regulate cortisol and influence the central nervous system.

Conclusion

This study, using patients with Cushing's disease as a model, explored the impact of prolonged high-concentration

cortisol exposure on human cognitive function. The findings revealed that individuals with prolonged high cortisol exposure commonly experience cognitive decline, with CORT AM/PM, COR-8am, BMI, and FPG identified as major risk factors for cognitive impairment. The nomogram model developed based on these risk factors demonstrated excellent predictive performance and clinical applicability in both the training and validation cohorts, providing an effective tool for the early identification of high-risk patients. These results not only confirmed the significant impact of prolonged high cortisol exposure on the central nervous system but also highlighted the critical role of metabolic factors in this process, emphasizing the multifactorial mechanisms of cognitive impairment. These findings offer a scientific basis for managing the cognitive health of Cushing's disease patients and provide important insights for prevention and treatment strategies for other cortisol-related conditions, such as chronic stress and metabolic syndrome.

Acknowledgments

We thank the patient for granting permission to publish this information. We appreciate all the team members who have shown concern and provided treatment advice for this patient the Chinese People's Liberation Army (PLA) General Hospital.

ORCID iDs

Yuxiang Sun  <https://orcid.org/0009-0001-9533-5334>
Shiyu Feng  <https://orcid.org/0000-0002-2267-4386>

Ethical considerations

This study was approved by the Ethics Committee of the Chinese PLA General Hospital (Approval No. [S2021-67701]).

Consent to participate

All participants provided written informed consent prior to inclusion in the study.

Author contributions

Yuxiang Sun: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Resources; Software; Supervision; Validation; Visualization; Writing – original draft.

Junpeng Xu: Conceptualization; Data curation; Formal analysis; Methodology; Project administration; Resources; Software; Supervision; Validation; Visualization.

Xiaoque Zheng: Data curation; Formal analysis; Investigation; Resources; Visualization; Writing – original draft.

Chunhui Li: Writing – review & editing.

Dongsheng Kong: Data curation; Formal analysis; Software; Supervision.

Qijia Wu: Investigation; Software; Validation.

Zihao Zhu: Investigation.

Shiyu Feng: Methodology; Project administration; Writing – original draft; Writing – review & editing.

Yanyang Zhang: Formal analysis; Methodology; Writing – review & editing.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by the National Natural Science Foundation of China (Grant Nos. 82001798 to Xinguang Yu; Grant Nos. 81871087 to Yanyang Zhang) and the Young Talent Project of Chinese PLA General Hospital (Grant Nos. 20230403 to Yanyang Zhang).

Declaration of conflicting interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Data availability statements

Data are available from the corresponding authors on reasonable request.

References

1. Wu JL, Li ZM, Chen H, et al. Distinct septo-hippocampal cholinergic projections separately mediate stress-induced emotional and cognitive deficits. *Sci Adv* 2024; 10: eado1508.
2. Cathomas F, Lin HY, Chan KL, et al. Circulating myeloid-derived MMP8 in stress susceptibility and depression. *Nature* 2024; 626: 1108–1115.
3. Kinlein SA, Phillips DJ, Keller CR, et al. Role of corticosterone in altered neurobehavioral responses to acute stress in a model of compromised hypothalamic-pituitary-adrenal axis function. *Psychoneuroendocrinology* 2019; 102: 248–255.
4. Hales CA, Stuart SA, Griffiths J, et al. Investigating neuropsychological and reward-related deficits in a chronic corticosterone-induced model of depression. *Psychoneuroendocrinology* 2023; 147: 105953.
5. McEwen BS. Glucocorticoids, depression, and mood disorders: structural remodeling in the brain. *Metabolism* 2005; 54: 20–23.
6. Pruessner M, Pruessner JC, Hellhammer DH, et al. The associations among hippocampal volume, cortisol reactivity, and memory performance in healthy young men. *Psychiatry Res* 2007; 155: 1–10.
7. Tournikioti K, Alevizaki M, Michopoulos I, et al. Differential association of cortisol with visual memory/learning and executive function in bipolar disorder. *Psychiatry Res* 2022; 307: 114301.
8. Knezevic E, Nenic K, Milanovic V, et al. The role of cortisol in chronic stress, neurodegenerative diseases, and psychological disorders. *Cells* 2023; 12: 2726.
9. Xing C, Zhou Y, Xu H, et al. Sleep disturbance induces depressive behaviors and neuroinflammation by altering the circadian oscillations of clock genes in rats. *Neurosci Res* 2021; 171: 124–132.

10. Nie D, Wang D, Wang Z, et al. The gut microbiome in patients with Cushing's disease affects depression- and anxiety-like behavior in mice. *Microbiome* 2024; 12: 225.
11. Katragadda A, Kunadia J, Kirsch P, et al. Cognitive decline in Cushing's syndrome: a systematic review. *J Neuroendocrinol* 2025; 37: e13466.
12. Ragnarsson O, Berglund P, Eder DN, et al. Long-term cognitive impairments and attentional deficits in patients with Cushing's disease and cortisol-producing adrenal adenoma in remission. *J Clin Endocrinol Metab* 2012; 97: E1640–1648.
13. Fernandes MA, Hickie SD, Penna S, et al. Comparative analysis of cognitive and psychiatric functioning in people with Cushing's disease in biochemical remission and people with nonfunctioning adenomas. *Behav Neurol* 2024; 2024: 4393169.
14. Yun SY, Yun JY, Lim C, et al. Exploring the complex link between obesity and intelligence: evidence from systematic review, updated meta-analysis, and Mendelian randomization. *Obes Rev* 2024; 25: e13827.
15. Le GH, Kwan A, Guo Z, et al. Impact of elevated body mass index (BMI) on cognitive functioning and inflammation in persons with post-COVID-19 condition: a secondary analysis. *Acta Neuropsychiatr* 2024; 36: 211–217.
16. Monserrat-Mesquida M, Quetglas-Llabrés M, Bouzas C, et al. Peripheral blood mononuclear cells oxidative stress and plasma inflammatory biomarkers in adults with normal weight, overweight and obesity. *Antioxidants (Basel)* 2021; 10: 813.
17. Neto A, Fernandes A and Barateiro A. The complex relationship between obesity and neurodegenerative diseases: an updated review. *Front Cell Neurosci* 2023; 17: 1294420.
18. Jing J, Liu C, Zhu W, et al. Increased resting-state functional connectivity as a compensatory mechanism for reduced brain volume in prediabetes and type 2 diabetes. *Diabetes Care* 2023; 46: 819–827.
19. González P, Lozano P, Ros G, et al. Hyperglycemia and oxidative stress: An integral, updated and critical overview of their metabolic interconnections. *Int J Mol Sci* 2023; 24: 9352.
20. Zhang S, Zhang Y, Wen Z, et al. Cognitive dysfunction in diabetes: abnormal glucose metabolic regulation in the brain. *Front Endocrinol (Lausanne)* 2023; 14: 1192602.
21. Logan RW and McClung CA. Rhythms of life: circadian disruption and brain disorders across the lifespan. *Nat Rev Neurosci* 2019; 20: 49–65.
22. Chan KL, Poller WC, Swirski FK, et al. Central regulation of stress-evoked peripheral immune responses. *Nat Rev Neurosci* 2023; 24: 591–604.
23. Arnaldi G, Angeli A, Atkinson AB, et al. Diagnosis and complications of Cushing's syndrome: a consensus statement. *J Clin Endocrinol Metab* 2003; 88: 5593–5602.
24. Agorastos A and Chrousos GP. The neuroendocrinology of stress: the stress-related continuum of chronic disease development. *Mol Psychiatry* 2022; 27: 502–513.
25. Shin HS, Lee SH, Moon HJ, et al. Prolonged stress response induced by chronic stress and corticosterone exposure causes adult neurogenesis inhibition and astrocyte loss in mouse hippocampus. *Brain Res Bull* 2024; 208: 110903.
26. de Leeuw M, Verhoeve SI, van der Wee N, et al. The role of the circadian system in the etiology of depression. *Neurosci Biobehav Rev* 2023; 153: 105383.