

# Determinants of anxiety and depression among pheochromocytoma patients

## A case–control study

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### Abstract

Phaeochromocytomas are catecholamine-producing neuroendocrine tumors that may manifest in many ways, specifically as sustained or paroxysmal hypertension. Data, including data from mental status screening, were prospectively collected from suspected patients. The Hospital Anxiety and Depression Scale was used as a screening tool to identify abnormal mental status. Results showed phaeochromocytoma patients were more likely to experience anxiety and depression. For future phaeochromocytoma treatment, early screening for anxiety and depression should be recommended.

**Abbreviations:** CT = computed tomography, EPV = expressed in terms of events per variable, HADS = Hospital Anxiety and Depression Scale, MRI = magnetic resonance imaging, n = number (), NAc = nucleus accumbens, POTS = postural orthostatic tachycardia syndrome, RMB = Ren Min Bi, SD = standard deviation.

**Keywords:** anxiety, depression, HADS, phaeochromocytomas

### 1. Introduction

Phaeochromocytomas are catecholamine-producing neuroendocrine tumors that originate in chromaffin cells in the adrenal medulla or extra-adrenal paraganglia.<sup>[1]</sup> In the general popula-

tion, the estimated annual incidence of phaeochromocytoma is 3 per million.<sup>[2]</sup> However, in the hypertension population, the proportion of phaeochromocytoma is 0.1% to 0.6%.<sup>[3]</sup> Despite their low prevalence, phaeochromocytomas are associated with a high mortality rate and several complications.<sup>[4]</sup>

An abnormal mental status has a major influence on cancer patients and could result in the impairment of the immune response, prolonged recovery times, difficulty with symptom control, poor compliance with treatment, and high mortality.<sup>[5,6]</sup> Many articles have verified that depression and anxiety disorders are more common among individuals affected by other cancers than the general population.<sup>[7,8]</sup> However, few studies have particularly explored the mental status of phaeochromocytoma patients. The common manifestations of phaeochromocytoma include unpredictable hypertension with an unexpected onset or recurrent events, significantly affecting all domains of patients' life and resulting in personal, clinical, socioeconomic implications, a diminished quality of life, and more frequent psychological disturbances compared with the general population.

Two reasons may account for the abnormal mental status. First, the extra secretion of catecholamines can cause various clinical symptoms, such as hypertension, light-headedness, syncope, and chronic fatigue. Such "spells" are characteristic manifestations of phaeochromocytomas and start with a sense of shortness of breath, followed by palpitations and a throbbing headache. These "spells" are often accompanied by symptoms of cold peripheries and facial pallor. These symptoms have repercussions for patients' daily lives and could render patients more vulnerable to experiencing unique psychosocial stressors. Second, catecholamine disruption may cause deficits in the medial frontal cortical regions and amygdala. Dysfunctions in these cortical regions are the basis of anxiety and depression.<sup>[5]</sup> These symptoms might cause and aggravate patients' psychological disease. Therefore, it is important to regularly screen and properly manage patients' psychological disorders.

The objective of this study was to identify the proportion of depression and anxiety in phaeochromocytoma patients.

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YJ and QX contributed equally to this work.

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study complied with the Declaration of Helsinki and was approved by Ethics Committees of the Third Hospital of Hebei medical university. Except for illiterate patients, all patients provided written informed consent. Illiterate patients indicate their consent by "making their mark" on the consent form, which were consistent with the local law.

The authors have no interests ethical, legal, and financial conflicts related to the article. All authors read and approved the manuscript to publish.

All of the materials were provided by the Third Hospital of Hebei medical university, and anyone can obtain the materials with appropriate reasons.

The authors declare that they have no conflict of interest.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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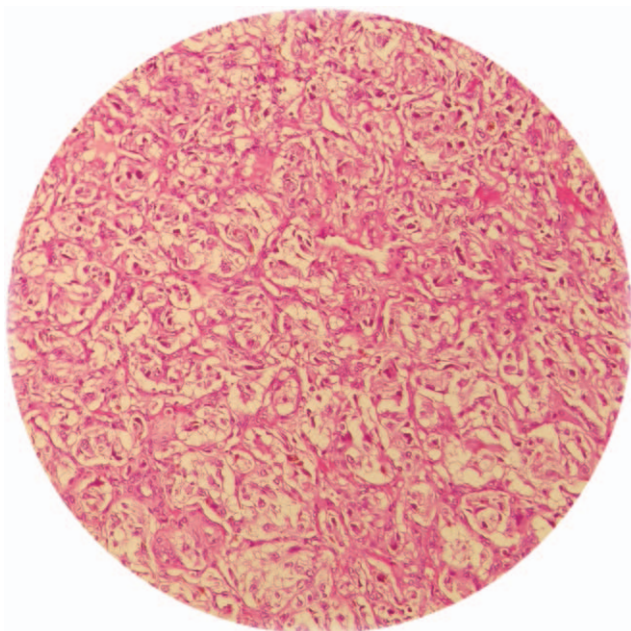
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Furthermore, we aimed to explore the factors associated with the risk of depression and anxiety in pheochromocytoma patients.

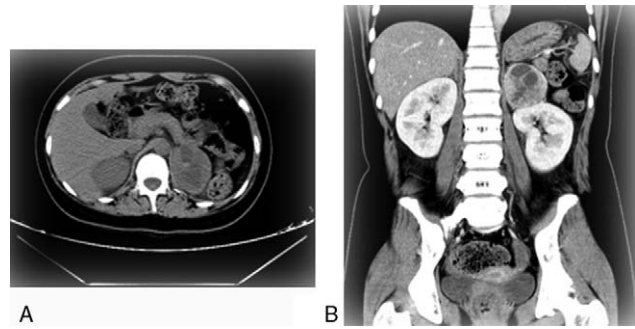
## 2. Methods

### 2.1. Patients and design

From January 2010 to May 2019, pheochromocytoma patients were recruited from the department of urological surgery at an academic teaching hospital in China. The academic teaching hospital receives pheochromocytoma patients from the entire country. For our study, sample size is typically expressed in terms of events per variable (EPV). An EPV of 10 is widely used as the lower limit for developing models that predict a binary outcome.<sup>[9]</sup> The sampling method used in this study was convenient sampling. The diagnosis should be made based on a combination of biochemical tests, imaging localization and biopsy. On the basis of clinical suspicion, 24-hour urinary total metanephrines and catecholamines were used as an initial screening test. The imaging localization of pheochromocytoma should be performed only after a biochemical diagnosis has been confirmed. At least 1 imaging examination, including computed tomography (CT) and magnetic resonance imaging (MRI), was used for the anatomic localization. The typical computed tomography imaging of pheochromocytoma patients is shown in Figure 1. After preoperative medical management, the surgeon removed the tumor and performed a pathological examination. The confirmed diagnosis depends on biopsy. The variable morphology of pheochromocytoma pathological sections reveals chief cells with an abundant granular cytoplasm and large vesicular nuclei and basophilic to amphophilic cells (Fig. 2).<sup>[2]</sup> For the case-control analysis, we randomly selected healthy volunteers as controls. The control volunteers were matched to the study patients by age and gender in a 2:1 ratio (n=156). The specific process is shown in Figure 3. Ethical



**Figure 1.** Typical computed tomography imaging of pheochromocytoma.



**Figure 2.** Typical histopathology of pheochromocytoma.

approval was granted by the Ethics Committees of the Third Hospital of Hebei medical university.

The patient inclusion criteria for this study were as follows: patients diagnosed with pheochromocytoma and the ability to write and read Chinese fluently. The exclusion criteria were as follows: an age <18 years; patients with other active cancers; patients confirmed to have other psychiatric problems; patients with intellectual and/or cognitive impairments or an inability to provide written informed consent; and pregnant and lactating women because these patients own a high risk of depression and anxiety, involving these patients could distort the results.<sup>[10]</sup>

### 2.2. Demographics and clinical evaluation

The Chinese-translated pilot-tested version of the Hospital Anxiety and Depression Scale (HADS) (14-item) was used to assess the mental status of the pheochromocytoma patients and control volunteers.<sup>[11]</sup> To avoid the effect of the operation on the patients' mental state, the HADS was performed at the time of admission. All mental status examinations were performed by the same attending psychiatrist. The HADS results were stored in a privacy-protected electronic medical record system. After pheochromocytoma was confirmed by surgical findings and pathologic results, we reviewed the patient data and analyzed their information. The HADS contains the following two 7-item subscales: HADS Depression and HADS Anxiety. Scores of 8 or above are indicative of a probable disorder, and scores of 7 and below indicate no disorder. Validated HADS in Chinese was used for interviewing our participants.<sup>[12]</sup> The Chinese translated version of HADS demonstrated satisfactory linguistic equivalence, conceptual equivalence, and scale equivalence (concordance rates at the cutoff of 8 for anxiety and depression subscales were 89.0% and 87.0%, respectively, and at the cutoffs of 11 were 87.0% and 91.0%, respectively) with English version.<sup>[12]</sup>

The participants (including the pheochromocytoma patients and control volunteers) provided their sociodemographic information, including age, marital status, socioeconomic status, educational level, gender, and job status. According to the annual household income, socioeconomic status was divided into the following 3 classes: high = earning more than 10,000 Ren Min Bi (RMB), medium = earning 50,001 to 10,000 RMB per year, or low = earning 1 to 5000 RMB per year.

By reviewing the medical records, the following clinical data of the pheochromocytoma patients were collected: hypertension, diabetes mellitus, cardiovascular events, neurological complications, alcohol use, tobacco use, and duration of symptoms.

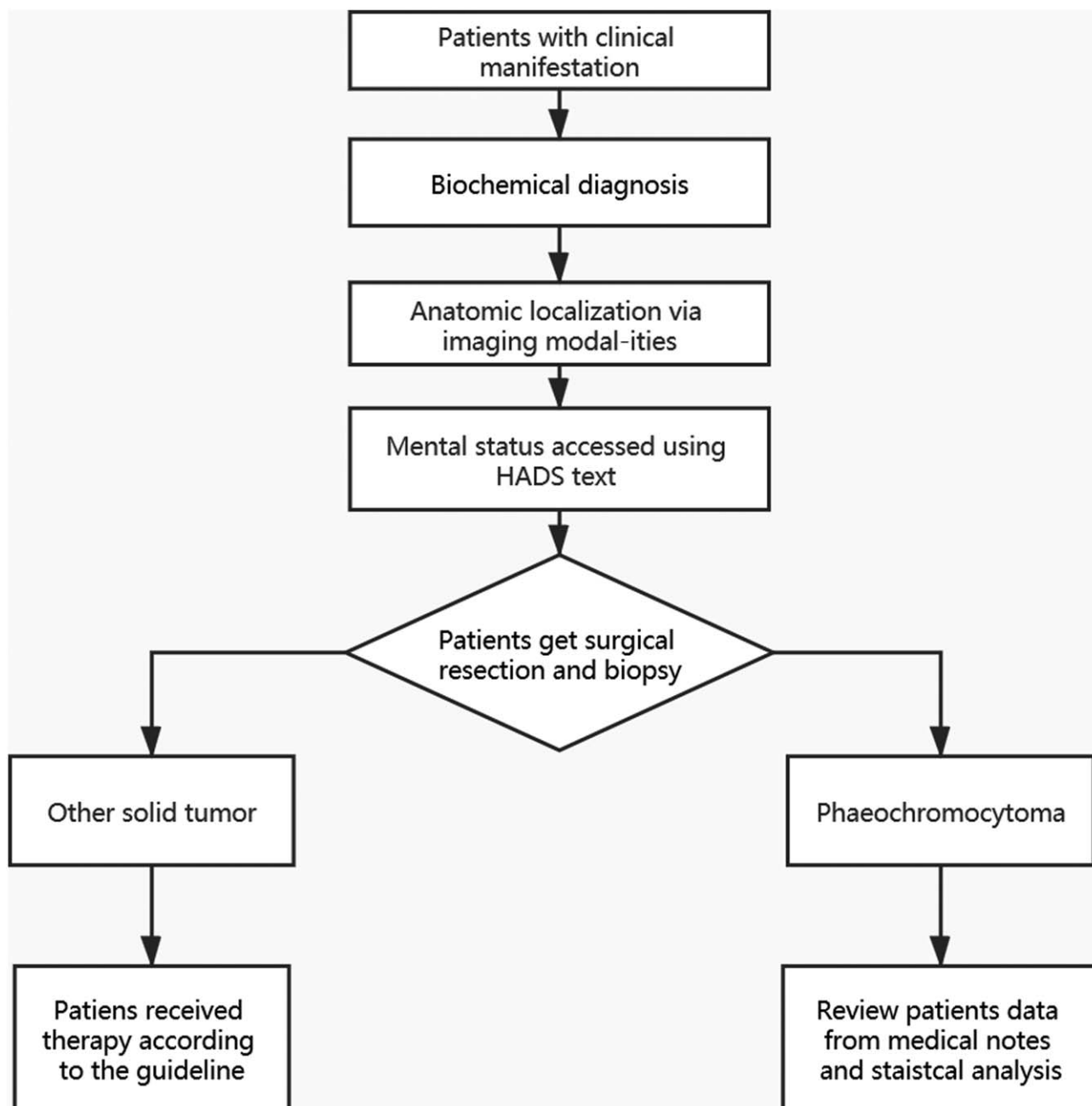


Figure 3. Selection of patient data for the analysis.

Hypertension can be paroxysmal hypertension, persistent hypertension, or orthostatic hypotension. On the basis of 2013 ESH/ESC Guidelines for the management of arterial hypertension,<sup>[13]</sup> the hypertension was categorized into 3 grades, including grade 1 (systolic pressure 140–159 mm Hg; diastolic pressure 90–99 mm Hg), grade 2 (systolic pressure 160–179 mm Hg; diastolic pressure 100–109 mm Hg), and grade 3 (systolic pressure  $\geq$ 180 mm Hg; diastolic pressure  $\geq$ 110 mm Hg). Cardiovascular events include arrhythmias, heart failure, baroreflex failure, and ischemic heart disease. Neurological complications included stroke, meningioma, diencephalic epilepsy, migraine, and postural orthostatic tachycardia syndrome

(POTS). In the control group, the clinical data were collected by self-reporting.

### 2.3. Statistical analyses

The research data were statistically analyzed with IBM SPSS for Windows (version 22.0, SPSS Inc., Chicago, IL). The mean, number (N), standard deviation (SD), and percentage (%) were used to describe the pheochromocytoma patients' characteristics (independent variables). Chi-squared tests were used to compare the proportion of depression or anxiety between the pheochromocytoma group and control group.

The occurrences of depression and anxiety were used as the outcomes (dependent variables) of the research. The odds ratio and 95% confidence intervals were used as measures of the associations. The associations between potential prognostic determinants and the outcomes were examined using a univariate logistic regression analysis. Predictors univariably associated with the outcome ( $P < .05$ ) were included in the multiple-predictor logistic regression model. Our study also retrieved the previous literature. Clinically relevant variables were also included in the multiple-predictor logistic regression model. The Pearson correlation coefficient statistic was used to assess multicollinearity.<sup>[14]</sup> The overall significance of the model was assessed using the -2 log-likelihood ratio test. We also used the Hosmer–Lemeshow goodness-of-fit Chi-square test to assess the fit of the model. Some diagnostic statistics against predicted values were created to explore the outliers and detect the influential observations by using the estimated values and Pearson and deviation residuals.<sup>[14]</sup> All reported  $P$ -values were 2-tailed, and a  $P$ -value under .05 was considered statistically significant.

### 3. Results

In total, 215 patients diagnosed with pheochromocytoma were recruited for this study. Final analysis was done on 194 patients, the remaining 21 patients having refused to participate. The response rate was 90.2%. In total, 156 individuals were included in the control group. The demographic and clinical characteristics of the 2 groups are summarized in Table 1. The proportion of depression was 32.5% in the pheochromocytoma patient group and 5.7% in the control group ( $P < .001$ ). The proportion

of anxiety was 26.8% in the pheochromocytoma patient group and 4.2% in the control group ( $P < .001$ ).

In the univariable logistic regression analyses, job status ( $P = .015$ ), gender ( $P = .008$ ), alcohol use ( $P = .041$ ), and duration of symptoms ( $P = .000$ ) were associated with depression at  $P < .05$ . Similar to the HADS depression subscale, the duration of symptoms ( $P = .025$ ), hypertension ( $P = .034$ ), and cardiovascular events ( $P = .028$ ) were associated with anxiety at  $P < .05$  (Table 2).

In the multiple-predictor logistic regression analysis, the duration of symptoms was an independent factor associated with depression [odds ratio (OR)=4.091, confidence interval (CI) 1.347–12.421,  $P = 0.013$ ] (Table 3). After adjusting for all covariates, the patients with hypertension (OR=1.426, CI 1.018–1.998,  $P = .0039$ ), cardiovascular events (OR=0.152, CI 0.032–0.717,  $P = .001$ ), and a long duration of symptoms (OR=2.871, CI 1.291–6.386,  $P = .010$ ) were more likely to have a diagnosis of anxiety (Table 4).

### 4. Discussion

In this case–control study, we assessed the proportion of anxiety and depression in pheochromocytoma patients. The HADS is a screening instrument used to identify patients at a high risk of developing depression and anxiety. The results showed that compared with the general adult population, the pheochromocytoma group had a higher proportion of anxiety and depression. In recent years, increasing interest has been placed on the mental status of cancer patients, and emotional distress has been recognized as the sixth vital sign in cancer care.<sup>[15]</sup> An abnormal mental status in many solid tumor patients, such as breast cancer and kidney cancer, is increasingly concerning, but limited attention has been paid to pheochromocytoma.<sup>[16,17]</sup> Patients' mental status is fundamental to the development of appropriate interventions because patients with comorbid psychological disorders tend to have severe symptoms, poorer outcomes, and greater use of healthcare resources. Given the frequent co-occurrence of anxiety and depression in pheochromocytoma patients, paying more attention to their mental status and optimizing the management of this comorbidity are essential.

Pheochromocytomas are catecholamine-secreting vascular and neuroendocrine tumors. Abnormal catecholamine secretion is the material foundation of mental disease. Catecholamines include norepinephrine, epinephrine, and dopamine. The dysfunction of the noradrenergic system has been confirmed as the principal cause of depression and anxiety disorders.<sup>[18]</sup> The amygdala is a potential site of noradrenergic/cholinergic interaction. Noradrenergic signaling through  $\alpha 2A$  receptors in neurons in the amygdala is critical for the regulation of depression and anxiety disorders. The nucleus accumbens (NAc) is a major component of the brain's reward system, and dopamine directly activates the NAc and affects mood. In patients with mood disorders, fluctuations in dopamine levels and dysfunction of the NAc have been observed.<sup>[19]</sup>

On the basis of these results, the duration of symptoms was an independent risk factor associated with depression and anxiety. A long duration of abnormal symptoms (more than 2 years), including an unexpected onset or recurrent events, significantly affects all aspects of patients' life and could cause considerable distress. Therefore, for pheochromocytoma patients, early medical intervention and the prompt achievement of symptom remission could help improve their mental and physical well-

**Table 1**  
Demographic and clinical characteristics of study sample.

	Pheochromocytoma group (N=194)	Control group (N=156)	P
Age, yr	47.5±7.7	48.5±5.9	.075
Gender, n (%)			
Female	109 (56.2)	97 (62.2)	
Male	85 (43.8)	59 (37.8)	.256
Marital status, n (%)			
Married	133 (68.6)	102 (65.4)	
Single	1 (0.5)	0	
Divorced	39 (20.1)	29 (18.6)	
Widowed	21 (10.8)	25 (16.0)	.421
Education, n (%)			
University	76 (39.2)	80 (51.3)	
Primary and middle	93 (47.9)	56 (35.9)	
Illiterate	25 (12.9)	20 (12.8)	.055
Job status, n (%)			
Unemployed (%)	24 (12.4)	30 (19.2)	
Employed	170 (87.6)	1126 (80.8)	.077
Socioeconomic status, n (%)			
High	31 (16.0)	29 (18.6)	
Medium	88 (45.4)	70 (44.9)	
Low	75 (38.6)	57 (36.5)	.798
Tobacco use, n (%)	12 (6.1)	9 (5.8)	.817
Alcohol limit, n (%)	15 (7.7)	13 (8.3)	.837
Dysrteriotony, n (%)	130 (67.0)	42 (26.9)	.000*
Diabetes mellitus, n (%)	101 (52.1)	26 (16.7)	.000*
Cardiovascular events, n (%)	24 (12.4)	0	.000*
Neurological complications, n (%)	152 (78.4)	0	.000*
Duration of symptoms, mo	14.5±8.2	NA	

\*  $P < .05$ .



**Table 2**  
Demographic and clinical factors association with depression and anxiety.

	N	Depression		P	Anxiety		P
		Present (n=63)	Absent (n=131)		Present (n=52)	Absent (n=142)	
Demographic characteristics							
Age, n (%)							
>50 years old	31	13 (20.6)	18 (13.7)	.220	10 (19.2)	21 (14.8)	.455
≤50 years old	163	50 (79.4)	113 (86.3)		42 (80.8)	121 (85.2)	
Gender, n (%)							
Female	109	44 (69.8)	65 (49.6)	.008*	27 (51.9)	82 (57.7)	.469
Male	85	19 (30.2)	66 (50.4)		25 (48.1)	60 (42.3)	
Marital status, n (%)							
Married	133	38 (57.1)	97 (74)	.062	41 (78.8)	92 (64.8)	.146
Single	1	0	1 (0.5)		0	1 (0.7)	
Divorced	39	16 (25.4)	23 (17.6)		5 (9.6)	34 (23.9)	
Widowed	21	11 (17.5)	10 (7.6)		6 (11.5)	15 (10.6)	
Education, n (%)							
University	76	25 (39.7)	51 (38.9)	.164	15 (28.8)	61 (43)	.186
Primary and middle	93	26 (41.3)	67 (51.1)		30 (57.7)	63 (44.4)	
Illiterate	25	12 (20.4)	13 (10.3)		7 (13.5)	18 (12.7)	
Job status, n (%)							
Unemployed (%)	24	13 (20.6)	11 (8.4)	.015*	4 (7.7)	20 (14.1)	.231
Employed	170	50 (79.4)	120 (91.6)		48 (92.3)	122 (85.9)	
Socioeconomic status, n (%)							
High	31	15 (23.8)	16 (12.2)	.093	12 (23.1)	19 (13.4)	.183
Medium	88	28 (44.4)	60 (45.8)		24 (46.2)	64 (45.1)	
Low	75	20 (31.7)	55 (42)		16 (30.8)	59 (41.5)	
Clinical characteristics							
Diabetes mellitus, n (%)	101	37 (58.7)	64 (48.9)	.197	23 (44.2)	78 (54.9)	.186
Blood pressure, n (%)							
Normal blood pressure	64	27 (42.9)	37 (28.2)	.055	19 (36.5)	45 (31.7)	.034*
Grade 1 hypertension	79	17 (27)	62 (47.3)		27 (51.9)	52 (36.6)	
Grade 2 hypertension	16	6 (9.5)	10 (7.6)		1 (1.9)	15 (10.6)	
Grade 3 hypertension	35	13 (20.6)	22 (16.8)		5 (9.6)	30 (21.1)	
Cardiovascular events, n (%)	24	8 (12.7)	16 (12.2)	.924	2 (3.8)	22 (15.5)	.028*
Neurological complications, n (%)	152	50 (79.4)	102 (77.9)	.812	42 (80.8)	110 (77.5)	.621
Tobacco use, n (%)	12	6 (9.5)	6 (4.6)	.181	4 (7.7)	8 (5.6)	.598
Alcohol use, n (%)	14	8 (12.7)	6 (4.6)	.041	4 (7.7)	10 (7)	.877
Duration of symptoms, n (%)							
>1 yr	39	23 (36.5)	16 (12.2)	.000*	16 (30.8)	23 (16.2)	.025*
≤1 yr	155	40 (63.5)	115 (87.8)		36 (69.2)	119 (83.8)	

Chi-squared test was used.

\* P<.05.

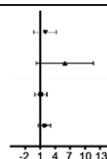
being. Hypertension is another factor independently associated with anxiety. Hypertension is the most common symptom of pheochromocytoma and widely varies. In most cases, hypertension is stable and permanent; however, it is also paroxysmal with wide fluctuations and resistant to treatment.<sup>[20]</sup> Long-term hypertension can cause extremely serious damage and influence

people’s lives and is detrimental to physical and mental health. Therefore, in the treatment process, better control of blood pressure should be given particular attention.

This study has several limitations. First, this study had a small sample size, and the current results may not be entirely applicable to other institutions because patient sociodemographic informa-

**Table 3**  
Logistic regression for variables associated with depression.

Variable	βvalue	Odds ratio (95% CI)	P
Gender	0.439	1.551 (0.760–3.164)	.227
Job status	−0.422	0.656 (0.173–2.486)	.535
Duration of symptoms	1.409	4.091 (1.347–12.421)	.013*
Alcohol	0.137	1.147 (0.290–4.542)	.845



\* P<.05.

**Table 4****Logistic regression for variables associated with anxiety.**

Variable	$\beta$ value		Odds ratio (95% CI)	P
Duration of symptoms	1.055		2.871 (1.291–6.386)	.010*
Cardiovascular events	−1.884		0.152 (0.032–0.717)	.017*
Hypertension	0.355		1.426 (1.018–1.998)	.039*

\*  $P < .05$ .

tion and clinical characteristics could differ across countries. Second, causality cannot be determined from the logistic regression model. Further longitudinal studies are needed to verify the present research conclusions. Finally, the anxiety and depression symptoms were measured only once, which could affect the accuracy of the research.

## 5. Conclusion

Phaeochromocytoma patients were at a higher risk of anxiety and depression. The early detection of mental health problems is beneficial for improving treatment outcomes. Phaeochromocytoma care has historically heavily focused on the cure of the disease; however, the psychosocial outcomes of cancer care should not be ignored. Furthermore, it should be recommended that screening for depression and anxiety is included in the standard of care for phaeochromocytoma patients.

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**Writing – original draft:** yuqing jiang.

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