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Predictors of postoperative recurrence of pheochromocytoma: a monocentric study

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Abstract

Objective To discuss the risk factors affecting the recurrence of pheochromocytoma (PCC) following surgery.

Methods We retrospectively reviewed patients who were hospitalized and underwent surgery for PCC between January 2012 and December 2020 at Chinese People's Liberation Army (PLA) General Hospital. Inclusion criteria were pathological diagnosis of PCC and availability of follow up.

Results In total, 451 patients met the inclusion criteria. The average age was 45.89 years, and the median tumor diameter was 5.75 cm. The mean recurrence time was 34.24 months. Of the 451 patients receiving surgery, there were 35 recurrent cases (7.85%). The univariate test showed that age, hypertension, history of PCC recurrence, Ki-67 index ≥ 5, bilateral tumor, duration of phenazopyridine administration, DBP at admission, open operation, intraoperative HR minimum, the number of episodes of intraoperative HR over 120 bpm, the number of episodes of intraoperative hemodynamic instability, and intraoperative bleeding were associated with recurrence after surgery. Multivariate COX regression analysis of age (hazard ratio 0.95), hypertension (hazard ratio 7.14), history of PCC recurrence (hazard ratio 69.35), family history of hypertension (hazard ratio 16.30), bilateral tumor (hazard ratio 7.38), tumor size (hazard ratio 1.05), the number of episodes of hemodynamic instability (hazard ratio 114.91) and duration of intraoperative instability (hazard ratio 1.12) were the independent risk factors on recurrence following surgery.

Conclusions Age, hypertension, history of PCC recurrence, family history of hypertension, bilateral tumor, tumor size, the number of episodes and the duration of intraoperative hemodynamic instability were independent risk factors on recurrence following surgery.

Clinical trial number Not applicable.

Keywords Pheochromocytoma, Recurrence, Risk factors, Epidemiology

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Introduction

Pheochromocytomas (PCC) are tumors originating from chromophores in the adrenal medulla and account for 80–85% of pheochromocytomas and paragangliomas [1]. They have catecholamine hormonal activity and mainly synthesize, secrete and release large amounts of catecholamine (CA), such as norepinephrine(NE), epinephrine(E) and dopamine(DA), causing a series of clinical syndromes such as increased blood pressure and metabolic changes, causing serious complications in the heart, brain, kidneys and blood vessels, and even becoming a major cause of death in patients. In the 4th edition of the 2017 classification of endocrine tumors [2], the WHO suggests that all pheochromocytomas/paragangliomas have metastatic potential and recommends that pheochromocytomas/paragangliomas be classified as metastatic and nonmetastatic, rather than malignant and benign [3]. The risk factors for recurrence or metastasis of PCC have been discussed only rarely, and the results are also controversial. Most articles [4–9] reported that age, gene mutation and tumor size are independent risk factors, but these studies included limited samples. In this study, we investigated the differences in clinical parameters between patients with and without recurrence by following up with pheochromocytoma resection patients in our center, which may enable urologists to accurately counsel urological patients when predicting postoperative recurrence following surgery.

Evidence acquisition

Objectives

The primary objective of this review was to identify the risk factors affecting the recurrence of pheochromocytoma after surgery.

Patient selection

Patients who were hospitalized and underwent tumor resection for PCC at our center from January 2012 to December 2020 were selected. Inclusion criteria were as follows: (1) clear diagnosis of PCC by postoperative pathology; (2) cooperation in the follow-up process; and (3) postoperative pathology suggested complete removal of the tumor. Exclusion criteria were as follows: (1) did not receive primary foci surgery; (2) incomplete medical records; and (3) lost in the follow-up process. In total, 451 patients met the inclusion criteria.

Methods

(1) Data collection included the following: We prospectively collected data on demographics and clinical/pathological characteristics, including age, sex, body mass index (BMI), comorbidities (hypertension, diabetes), history of pheochromocytoma recurrence, family history of hypertension, tumor size, and catecholamine levels (norepinephrine, epinephrine, dopamine). A subset of patients underwent Ki-67 testing. However, due to individualized treatment strategies and financial constraints, some patients did not undergo immunohistochemical evaluation. Preoperative blood pressure management included daily phenoxybenzamine in patients with unstable preoperative blood pressure. Patients initiated phenoxybenzamine at 10 mg/day, with incremental dose increases until blood pressure fell below 130/80 mmHg and heart rate ranged between 60 and 80 bpm, after which dose escalation ceased. We recorded the duration of phenoxybenzamine administration and calculated a cumulative dose index (dos*time/weight).

We also documented perioperative parameters, such as mode of operation, surgical approach, intraoperative bleeding volume, and preoperative/postoperative blood pressure and heart rate values (e.g., systolic blood pressure [SBP] at admission, diastolic blood pressure [DBP] at admission, maximum/minimum/mean arterial pressure [MAP], and maximum/minimum heart rate [HR]). Intraoperative hemodynamic instability was defined as SBP > 180 mmHg or > 130% of admission SBP, SBP < 80 mmHg or < 70% of admission SBP, or HR > 120 bpm. We counted the number of discrete episodes meeting these criteria in the anesthesia records. Since the anesthesia records are updated every 5 min, we set the minimum duration for each episode of instability to 5 min. Additionally, we summed the total time spent in instability to determine the duration of intraoperative hemodynamic instability.

The primary outcome was recurrence, defined as tumor reappearance on imaging (MRI or CT), including either local or distant metastases [7]. Postoperative imaging took place at our hospital or other facilities, with follow-up carried out via outpatient visits and/or telephone interviews. Formal follow-up began 6–12 months after surgery and was scheduled every three months for at least two years. Each follow-up included radiographic evaluations, and some also involved laboratory testing. All patients who completed imaging assessments at outside institutions were contacted by telephone to confirm their imaging findings and clinical status.

Statistical analysis

SPSS 26.0 statistical software was used for data analysis. For quantitative variables, the normality was assessed using the Shapiro-Wilk test. If they followed a normal distribution, they were expressed as (mean ± standard deviation), and the independent samples t-test was employed for intergroup comparisons. Non-normally distributed quantitative variables were represented as median (interquartile range), and group comparisons were conducted using the Wilcoxon rank sum test. The chi-square test was employed to assess the difference

in occurrence proportions of qualitative data between groups. Finally, 12 datasets were chosen for univariate and multivariable COX regression analysis to derive the Hazard Ratio (Exp(B)), with recurrence considered as a time-dependent factor. A significance level of $p < 0.05$ was deemed statistically significant.

Results

Baseline characteristics of the cohort and percentage of recurrences

The mean age of the 451 patients who underwent pheochromocytoma resection was 45.89 ± 14.417 years, with 229 (50.80%) were male and 222 (49.20%) were female. The prevalence of hypertension among patients was 55.21%, with a median tumor size/diameter of 5.75 cm. Throughout the follow-up period, there were 35 cases of recurrence (7.85%) and two deaths, one from natural causes and one from lymphoma, with neither directly linked to pheochromocytoma. The average time to recurrence was 34.24 months.

Characteristics of the demographics, clinical and pathological profiles of patients with pheochromocytoma following pheochromocytoma resection

Following statistical analysis, patients experiencing postoperative recurrence tended to be younger [36.54 ± 14.41 years compared to 47.61 ± 0.83 years, $p < 0.001$], exhibited a higher prevalence of combined hypertensive [26 cases (10.4%) compared to 9 cases (4.5%), $p = 0.018$] and demonstrated a greater incidence of previous pheochromocytoma recurrence [8 cases (42.1%) compared to 27 cases (6.25%), $p < 0.001$]. Moreover, patients with postoperative recurrence were more likely to present with bilateral tumors [7 cases (17.5%) compared to 28 cases (6.8%), $p = 0.036$], and a Ki-67 index ≥ 5 [11 cases (31.43%) compared to 12 cases (34.29%), $p = 0.036$]. However, there was no significant difference in tumor size between the two groups. (Table 1)

Characteristics of perioperative data in patients following pheochromocytoma resection

Following statistical analysis, patients experiencing postoperative recurrence had a shorter duration of phenazopyridine administration [21.24 ± 12.77 days compared to 27.55 ± 16.35 days, $p = 0.044$] and exhibited higher diastolic blood pressure at admission [81.00 (77.25,92.25) mmHg compared to 80.00 (74.00,90.00) mmHg, $p = 0.046$]. Postoperative recurrence rate was higher among patients who underwent open surgery compared to those who underwent laparoscopic and robotic surgery [7 (21.9%) compared to 20 (6.3%) and 8 (8%), $p = 0.026$]. Patients with postoperative recurrence generally exhibited a lower minimum HR [65.22 ± 13.88 bpm compared to 58.09 ± 8.74 bpm, $p \leq 0.001$], a higher incidence of episodes of HR over 120 bpm [5 cases with the number ≥ 6 (29.41%) compared to 30 cases with the number ≥ 6 (6.91%), $p = 0.018$], a higher incidence of episodes of hemodynamic instability [4 cases with the number ≥ 8 (11.43%) compared to 5 cases with the number ≥ 8 (1.44%), $p = 0.018$], and greater intraoperative bleeding volume [175.0 ml (100.0,450.0) compared to 100.0 ml (50.0,275.0), $p = 0.018$]. However, no significant difference in recurrence rates was observed between patients who underwent laparoscopic and robotic surgeries. (Table 2)

Univariate and multivariate-factors COX analyses

The inclusion criteria of these 12 datasets were that univariate Cox analysis indicated clinical indicators that were not outcome-related and had a Pearson correlation coefficient less than 0.2, with efforts made to minimize the impact of human factors. Univariate and multivariate COX analyses were conducted to predict recurrence following surgery. The following variables were identified as independent prognostic factors for recurrence following surgery: age (hazard ratio 0.95 (0.91, 0.99), $p = 0.001$), hypertension (hazard ratio 7.14 (1.23,41.54), $p = 0.029$), history of PCC recurrence (hazard ratio 69.35 (7.97,603.73), $p < 0.001$), family history of hypertension (hazard ratio 16.30 (1.55,251.8), $p < 0.001$), bilateral tumor (hazard ratio 7.38 (1.04,52.24), $p = 0.045$), tumor size (hazard ratio 1.05 (1.04,2.60), $p = 0.031$), the number of episodes of intraoperative hemodynamic instability (hazard ratio 114.91 (1.68,7870.89), $p = 0.034$), and duration of intraoperative instability (hazard ratio 1.12 (1.02,1.25), $p = 0.025$). (Table 3)

K-M survival analysis

We attempted to utilize ROC curve analysis to evaluate the Youden index for continuous variables among independent influencing factors and to determine the diagnostic threshold. Specifically, we selected the value that maximized the sum of specificity and sensitivity as the diagnostic threshold. The analysis yielded an AUC of 0.692 for age, with a diagnostic threshold of 41.5 years. For tumor size, the AUC was 0.489, with a diagnostic threshold of 11.25 cm. Additionally, the AUC for the duration of intraoperative hemodynamic instability was 0.528, with a diagnostic threshold of 12.5 min (Figure S1).

Survival curve was generated using Kaplan-Meier (K-M) analysis for categorized independent risk factors and continuous variables treated with diagnostic critical values. Concurrently, the log-rank test was employed to assess survival differences. Statistical analysis revealed significant differences in survival curves for age (< 41.5 years) ($p = 0.0003$), hypertension as a comorbidity ($p = 0.014$), history of recurrence ($p < 0.0001$), bilateral tumors ($p = 0.0037$), tumor size (≥ 11.25 cm) ($p = 0.0032$),

Table 1 Patient demographics and clinical and pathological characteristics

Variables	Overall	No-recurrence ($n=416$)	Recurrence ($n=35$)	*P* value
Age(year)	45.89 ± 14.42	47.61 ± 0.83	36.54 ± 14.41	< 0.001*
Sex				0.543
male	229(50.80%)	209(50.20%)	20(57.1%)	
female	222(49.20%)	207(49.80%)	15(42.9%)	
BMI	24.49 ± 10.98	23.57 ± 13.43	23.56 ± 4.60	0.604
Hypertension				0.018
Present	249(55.20%)	223(53.60%)	26(74.30%)	
Absent	202(44.80%)	193(46.40%)	9(25.70%)	
Diabetes				0.643
Present	118(26.20%)	110(26.40%)	8(22.90%)	
Absent	333(73.80%)	306(73.60%)	27(77.10%)	
History of pcc recurrence				< 0.001*
Present	19(4.20%)	11(2.60%)	8(22.90%)	
Absent	432(95.80%)	405(97.40%)	27(77.10%)	
Family history of hypertension				0.098
Present	173(38.40%)	155(37.70%)	18(51.40%)	
Absent	278(61.60%)	261(62.30%)	17(48.60%)	
tumor size(cm)	5.0(3.5,7.0)	5.0(3.5,7.0)	6.0(5.8,6.8)	0.447
Ki-67 index				0.031*
< 5	225(49.89%)	213(51.20%)	12(34.29%)	
≥ 5	89(19.73%)	78(18.75%)	11(31.43%)	
Unknown	137(30.38%)	125(30.05%)	12(34.29%)	
Preoperative NE	277.9(111.3,556.2)	289.3(86.1,570.5)	250.1(178.6,739.8)	0.523
Preoperative E	41.7(14.7,121.9)	37.7(11.0,102.7)	80.9(29.4,164.9)	0.503
Preoperative DA	419.6(281.4,681.9)	395.3(277.4,654.9)	524.1(441.7,735.6)	0.124
Tumor side				0.036*#
left	195(43.20%)	182(43.80%)	14(48.10%)	
right	215(56.80%)	201(56.20%)	14(51.90%)	
Bilateral	33(8.90%)	25(7.90%)	7(20.00%)	
Unclassified	8(1.8%)	8(1.9%)	0	

BMI: Body Mass Index; NE: Norepinephrine; E: Epinephrine; DA: Dopamine

* Significant difference

p-value from statistical comparison between groups, significant difference observed between Bilateral and Unclassified groups

and the number of episodes of hemodynamic instability ≥ 8 ($p=00.13$). No significant differences were observed in survival curves for duration of hemodynamic instability (≥ 12.5 min) ($p=0.33$) or family history of hypertension ($p=0.2$). (Fig. 1)

Discussion

In conclusion, we observed that the recurrence rate among patients was 35 (7.8%), consistent with findings from previous research (between 1% and 34%, median 6%) [10, 11]. The independent samples test indicated that age, hypertension, history of PCC recurrence, Ki-67 index ≥ 5, bilateral tumor, duration of phenazopyridine administration, DBP at admission, open operation, intraoperative HR min, the number of episodes of intraoperative HR over 120 bpm, the number of episodes of intraoperative hemodynamic instability, and intraoperative bleeding volume were associated with recurrence following surgery. Multivariate COX regression analyses revealed that age, hypertension, history of PCC recurrence, family history of hypertension, bilateral tumor, tumor size, the number of episodes of intraoperative hemodynamic instability, and the duration of intraoperative hemodynamic instability were independent risk factors of recurrence following surgery. These findings were consistent with those reported in other articles [1, 4, 5, 8, 10–16]. The association of the duration of phenazopyridine administration, the number of episodes of intraoperative HR over 120 bpm, and intraoperative HR minimum with recurrence presents new insights that have not been emphasized in previous studies.

A 2016 meta-analysis [11], reported a negative correlation between age and recurrence rate. Similarly, our study found that age remained statistically significant in both univariate and multivariate analysis ($p<0.001$). Some study [1, 4, 5, 8, 12–16] suggested that younger patients had a higher risk of recurrence, while others [9, 17] indicated that elderly patients were more prone

Table 2 Patient perioperative characteristics

Variables	Overall	No-recurrence (*n* = 416)	Recurrence (*n* = 35)	t/u/x^2	*P* Value
Daily preoperative phenoxybenzamine dose (ml)	20.0(15.0,35.0)	20.0(12.5,35.0)	17.5(10.6,25.0)	-0.825	0.409
Duration of phenazopyridine administration (day)	26.0 ± 15.7	27.6 ± 16.4	21.2 ± 12.8	2.021	0.044*
Dos*time/weight	7.1(4.1,13.3)	7.5(4.4,13.1)	5.7(3.9,9.5)	-1.364	0.173
SBP at admission	130.0(120.0,142.5)	130.0(120.0,150.0)	127.0(120.0,140.0)	-0.714	0.475
DBP at admission	80.0(70.0,90.0)	80.0(70.0,90.0)	85.0(70.0,90.0)	-2.217	0.027*
Operation mode				7.267	0.026*
Open	32(7.10%)	25(6.00%)	7(20.00%)		
Laparoscopic	319(70.70%)	299(71.90%)	20(57.10%)		
Robotic	100(22.20%)	92(22.10%)	8(22.90%)		
Surgical approach				1.467	0.226
open	32(7.10%)	25(6.00%)	7(20.00%)		
Transperitoneal	109(26.00%)	99(25.30%)	10(35.70%)		
Retroperitoneal	310(74.00%)	292(74.70%)	18(64.30%)		
Postoperative SBP (mmHg)	120.0(110.0,130.0)	120.0(106.3,137.5)	120.0(110.0,135.0)	-0.406	0.684
Postoperative DBP (mmHg)	70.0(60.0,80.0)	70.0(60.0,80.0)	70.0(60.3,87.5)	-0.616	0.538
HR max	106.67 ± 17.40	106.43 ± 16.54	107.57 ± 20.58	-0.345	0.734
HR min	59.58 ± 10.40	58.09 ± 8.74	65.22 ± 13.88	-3.718	< 0.001*
HR range	47.08 ± 16.59	48.34 ± 16.35	42.35 ± 16.89	1.896	0.051
the number of episodes of intraoperative HR over 120 bpm				5.566	0.018*
< 6	434(96.23%)	404 (97.12%)	30 (85.72%)		
≥ 6	17(3.77%)	12 (2.88%)	5 (14.28%)		
One-time HR range	24.06 ± 12.34	23.85 ± 12.57	24.85 ± 11.58	-0.351	0.674
SBP max	163.01 ± 24.43	163.00 ± 24.48	163.09 ± 24.38	-0.020	0.984
SBP min	95.54 ± 13.94	95.50 ± 13.49	95.96 ± 17.77	-0.171	0.856
SBP range	66.88 ± 27.73	66.85 ± 27.23	67.13 ± 32.45	-0.061	0.955
One-time SBP range	45.73 ± 24.71	46.04 ± 23.77	42.94 ± 32.25	0.719	0.489
DBP max	90.10 ± 13.10	89.97 ± 13.23	91.25 ± 12.06	-0.543	0.589
DBP min	53.77 ± 8.62	53.68 ± 8.35	54.63 ± 10.84	-0.617	0.540
DBP range	35.49 ± 14.47	35.37 ± 14.37	36.62 ± 15.56	-0.476	0.633
One-time DBP range	22.88 ± 11.46	23.02 ± 11.41	21.62 ± 12.04	0.674	0.498
MAP max	110.44 ± 22.55	110.03 ± 23.26	114.22 ± 14.19	-1.027	0.305
MAP min	66.95 ± 14.02	66.62 ± 14.13	70.04 ± 12.69	-1.353	0.177
MAP range	43.49 ± 17.89	43.41 ± 17.66	44.18 ± 20.22	-0.234	0.815
the number of episodes of intraoperative hemodynamic instability				8.648	0.003*
< 8	442(98.00%)	411 (98.56%)	31 (88.57%)		
≥ 8	9(2.00%)	5 (1.44%)	4 (11.43%)		
Duration of intraoperative hemodynamic instability	16.94 ± 25.46	16.30 ± 22.99	22.59 ± 41.65	-1.364	0.173
Intraoperative bleeding (ml)	100.0(50.0,312.5)	100.0(50.0,275.0)	175.0(100.0,450.0)	-2.105	0.035*

SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; HR: Heart Rate; BPM: Beats Per Minute; MAP: Mean Arterial Pressure

* Significant difference

to recurrence. We speculated that younger patients are more prone to recurrence because they have a higher prevalence of germline mutations [12, 16, 18, 19] in tumors, which increases the likelihood of recurrence.

PCCs are rare tumors, with an estimated annual incidence of 3 per 1 million [20, 21]. However, the proportion of pheochromocytomas in the hypertensive population is between 0.1% and 0.6% [22]. According to our data, patient's hypertension as a comorbidity are more likely to experience recurrence following surgery. Moreover, elevated blood pressure levels (SBP at admission, DBP at admission and intraoperative MAP maximum) are associated with an increased risk of postoperative recurrence. Similar findings [9] showed the same result. We speculate that a possible reason is that hypertensive patients or patients with intraoperative hemodynamic instability may have higher tumor activity and malignancy, making recurrence more likely. Hypertension and intraoperative hemodynamic instability are known to be associated with increased sympathetic nervous system activity, which

Table 3 Univariate and multivariate analyses

Variables	Univariate analyses		Multivariate analyses	
	HR(95% CI)	*P* value	HR(95% CI)	*P* value
Age	0.95 (0.92, 0.97)	< 0.001*	0.95 (0.91, 0.99)	0.001*
Sex(female)	0.79 (0.39, 1.64)	0.532		
BMI	0.96 (0.88, 1.04)	0.310		
Drug dosage per day	0.99 (0.96, 1.02)	0.626		
Length of medication	0.96(0.92–0.99)	0.012*	1.01(0.91,1.12)	0.788
Hypertension	2.36 (1.18, 5.74)	0.018*	7.14 (1.23,41.54)	0.029*
Diabetes	0.71 (0.29, 1.73)	0.448		
History of PCC recurrence	10.20 (4.35, 23.91)	< 0.001*	69.35(7.97,603.73)	< 0.001*
Family history of hypertension	1.77(0.87,3.64)	0.118	16.30(1.55,251.8)	< 0.001*
Bilateral tumor	5.25 (2.23, 12.37)	0.001*	7.38(1.04,52.24)	0.045*
Left or right side	0.79 (0.35, 1.79)	0.568		
Ki-67 ≥ 5	1.07(1.00,1.14)	0.045*	26.70(0.13,5519.68)	0.227
SBP at admission	0.88(0.79,1.01)	0.339		
DBP at admission	1.03 (1.01, 1.06)	0.014*		
Surgery approach (open or not)	0.31 (0.13, 0.76)	0.011*	1.00(0.07,12.64)	0.999
Surgery approach (laparoscopic/robotic)	1.36 (0.53, 3.48)	0.519		
Surgery trans (transperitoneal/retroperitoneal)	0.56 (0.24, 1.33)	0.191		
Tumor size	1.06(0.92,1.21)	0.436	1.65(1.04,2.60)	0.031*
The number of episodes of intraoperative HR over 120 ≥ 6 bpm	4.32(1.28,14.65)	0.019*	121.43(0.03,584419.65)	0.267
the number of episodes of intraoperative hemodynamic instability ≥ 8	5.69(1.72,18.88)	0.005*	114.91(1.68,7870.89)	0.034*
duration of intraoperative hemodynamic instability	1.01(1.00,1.02)	0.121	1.12(1.02,1.25)	0.025*
HR range	0.99(0.97,1.01)	0.376		
One-time HR range	1.02(0.99,1.05)	0.134		
SBP range	1.00(0.99,1.02)	0.201		
One-time SBP range	1.00(0.99,1.01)	0.181		
DBP range	1.01(0.99,1.04)	0.294		
One-time DBP range	1.00(0.97,1.03)	0.969		
MAP range	1.01(0.99,1.03)	0.469		

BMI: Body Mass Index; NE: Norepinephrine; E: Epinephrine; DA: Dopamine. SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; HR: Heart Rate; BPM: Beats Per Minute; MAP: Mean Arterial Pressure

*** Significant difference**

could enhance catecholamine secretion from PCCs, potentially leading to more aggressive tumor behavior. **(Increased catecholamine secretion contributes to hypertension in TRPM4-deficient mice)** Additionally, elevated blood pressure may promote angiogenesis and increase the availability of nutrients to the tumor, fostering its growth and progression. (**Clinical significance of hypertension in patients with different types of cancer treated with antiangiogenic drugs**) Another potential mechanism could be the relationship between hypertension and higher tumor burden, as larger tumors may be more likely to invade surrounding tissues, thus increasing the risk of recurrence. Furthermore, the Ki-67 index, a marker of cell proliferation, and catecholamine secretion levels could provide additional insight into the tumor's proliferative activity in hypertensive patients, contributing to the increased likelihood of recurrence. Thus, it is crucial to explore these underlying mechanisms further to better understand how hypertension influences tumor behavior and recurrence in PCC patients.(**Clinical and Pathological Tools for Predicting Recurrence and/or Metastasis in Patients with Pheochromocytoma and Paraganglioma**).

Several studies [23–34] indicates that 25- 40% of patients diagnosed with PCC or paraganglioma carry known germline mutations, regardless of age at onset and family history. Our multivariate analyses revealed a significant association between recurrence and family history of hypertension in our patients, a finding consistent with a previous study [9]. This suggests a potential influence of family inheritance on the recurrence of PCC.

Research [9, 35] showed that, in addition to individuals predisposed to hereditary PCC, patients with a history of tumors removal constituted another high-risk group, which was consistent with our findings. We speculate that patients with a history of PCC recurrence may have a higher proportion of genetic mutations associated with heredity, making PCCs more aggressive and prone to recurrence.

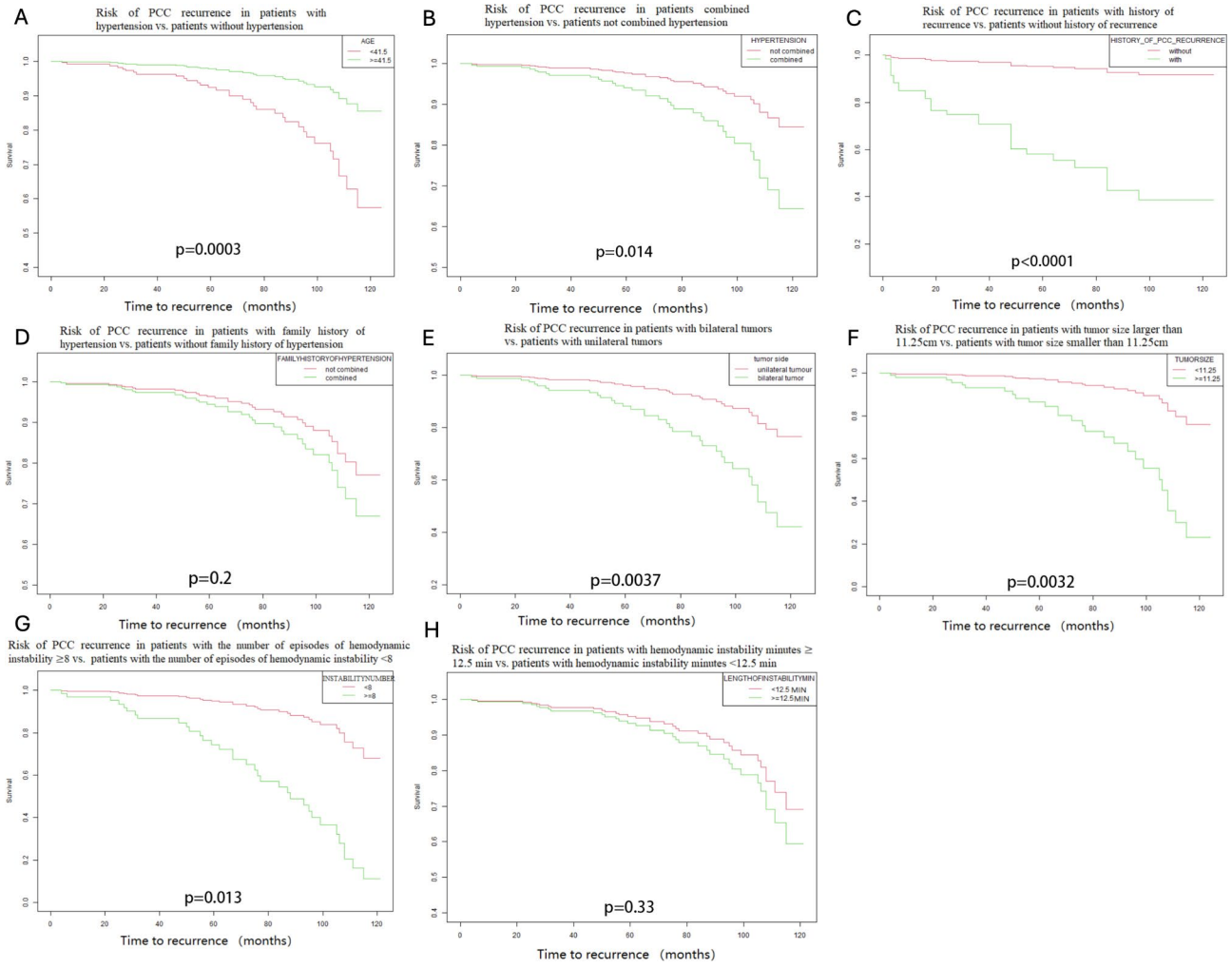

Fig. 1 K-M Survival Analysis (**A**. significant differences in survival curves for age (< 41.5 years) ($p = 0.0003$); **B**. significant differences in survival curves for hypertension as a comorbidity($p = 0.014$); **C**. significant differences in survival curves for previous history of recurrence ($p < 0.0001$); **D**. no significant differences in survival curves for family history of hypertension ($p = 0.2$); **E**. significant differences in survival curves for bilateral tumors ($p = 0.0037$); **F**. significant differences in survival curves for tumor size (≥ 11.25 cm) ($p = 0.0032$); **G**. significant differences in survival curves for the number of episodes of intraoperative hemodynamic instability ≥ 8 ($p = 0.013$); **H**. no significant differences in survival curves for instability minutes (≥ 12.5 min) ($p = 0.33$))

Our study also identified association between bilateral tumors and recurrence, consistent with findings from other studies [1, 9, 12–15, 21]. Bilateral tumor resection surgeries typically involve two procedures, thereby doubling the risk of damaging normal tissues and the chances of incomplete tumor removal during surgery. We speculate that this ultimately increases the likelihood of functional impairment and recurrence.

While previous studies have consistently identified tumor size as an independent predictor of recurrence [5, 6, 8, 10], our study found no association in univariate analysis but a significant correlation in multivariate analysis. This discrepancy may be due to our cohort's relatively large average tumor size (5.75 cm), which is substantially higher than the reported guideline/literature averages of 2.3–2.7 cm (median 48 mm) [11]. The limited variability in tumor size might have masked its effect in univariate analysis, while adjusting for confounders in the multivariate model revealed its prognostic impact. Moreover, surgical factors likely contribute to these findings: larger pheochromocytomas demand more complex resections, and our center's mature surgical techniques—evidenced by a lower positive margin rate compared to other institutions—likely ensured complete tumor removal. The limited variability in tumor size might have masked its effect in univariate analysis, while adjusting for confounders in the multivariate model revealed its prognostic impact. Moreover, surgical factors likely contribute to these findings: larger pheochromocytomas demand more complex resections, and our center's mature surgical techniques likely ensured complete tumor removal. Tumors detected through Von Hippel–Lindau disease screening tend to be smaller and less functional than sporadic cases, further complicating the association [4, 6, 7, 36]. Overall,

these results suggest that the prognostic value of tumor size on recurrence is multifactorial, depending on factors such as surgical method, surgeon expertise, and underlying tumor biology. Future studies should stratify patients by surgical approach and genetic background to better delineate these relationships.

Our findings on intraoperative characteristics revealed that both the number of episodes and the duration of intraoperative hemodynamic instability were independent risk factors, which has not been specifically addressed in other studies. There are limited articles discussing the relationship between intraoperative hemodynamics and recurrence. We hypothesize that hemodynamic instability may trigger catecholamine release, which in turn promotes an inflammatory response, affects tumor healing, and alters the tumor microenvironment, thereby creating favorable conditions for tumor recurrence. Most studies in this area suggest a close relationship between blood pressure fluctuations (from max to min) and recurrence. Additionally, some articles [37, 38] suggest that blood pressure instability increases the risk of postoperative complications and mortality. We quantified the instability of blood pressure, dividing it into height and width dimensions, and found that both showed significant differences, further supporting the significant impact of intraoperative blood pressure instability on disease recurrence.

This study found that the intraoperative HR minimum and the number of episodes of intraoperative HR over 120 bpm are also risk factors for recurrence. Although intraoperative heart rate variation is critical in surgical management, other studies may not have specifically identified the minimum intraoperative HR as a risk factor associated with postoperative recurrence. We hypothesize that the relationship with heart rate may be due to blood pressure fluctuations and the use of intraoperative medications, which cause heart rate changes and indirectly link to recurrence. This may also explain why these two factors no longer showed significance in the multivariate analysis.

Given several limitations, caution is warranted when interpreting the present findings. This was a retrospective observational study conducted at a single center, and some data were missing. Although we excluded samples with missing data in both univariate and multivariate Cox analyses, this led to potential selection bias. Therefore, further multi-center prospective studies with more complete data are needed for validation. Secondly, postoperative metanephrines levels were not obtained to confirm complete resection. Thirdly, the patients were not assessed for germline mutations, which may help pinpoint patients and siblings at higher risk for disease or recurrence. The missing genetic information also leads to the omission of the percentage of VHL (Von Hippel-Lindau) patients, and it prevents the validation of the hypothesis that younger patients are more likely to carry germline mutations that may contribute to recurrence. Lastly, the study included patients who had surgery less than 5 years before the study, and some of them had tumors that may not have experienced recurrence yet, which may underestimate the true recurrence rate, and affect the identification of risk factors, particularly those with a longer time to recurrence.

Conclusions

In the multivariate analysis, age, hypertension, history of PCC recurrence, family history of hypertension, bilateral tumor, tumor size, the number of episodes and the duration of intraoperative hemodynamic instability were independent risk factors on recurrence after pheochromocytoma resection. Ki-67 index ≥ 5, duration of phenazopyridine administration, DBP at admission, open operation, intraoperative HR min, the number of episodes of intraoperative HR over 120 bpm, and intraoperative bleeding volume were associated with recurrence following surgery. The findings of this study will facilitate doctors in providing to accurate counseling to patients after surgery for pheochromocytoma regarding the prediction of postoperative recurrence following surgery.

Supplementary Information

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Supplementary Material 1

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Author contributions

X.Z. and X.M. and B.W. made contributions to the conception and design of the work; Z.L., D.L., Y.J. and J.L. collected the Data; Z.L., D.L., L.T. and X.L. analyzed the data; Z.L. and X.L. wrote the main manuscript text. All authors have read and approved the manuscript.

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Data availability

The datasets generated and analysed during the current study are not publicly available due to privacy concerns and ongoing other research but are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The creation and retrospective review of our database was approved by ethics committee of Chinese PLA General Hospital, China, and, therefore, conforms to the ethical standards laid down in the 1964 Helsinki Declaration and its later amendments. This article does not contain any studies with animals

performed by any of the authors. Informed consent was obtained from all individual participants included in the study.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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