Risk factors for postoperative cardiovascular morbidity after pheochromocytoma surgery: a large single center retrospective analysis

Song Bai, Zichuan Yao, Xianqing Zhu, Zidong Li, Yunzhong Jiang, Rongzhi Wang and Ning Wen

Department of Urology, Shengjing Hospital of China Medical University, Shenyang 110004, China

Abstract. Surgical resection is the primary treatment strategy for pheochromocytoma; however, it carries a high risk of morbidity and mortality, especially with respect to cardiovascular complications, which is the most common kind of morbidity. The risk factors for morbidity remain unclear and require further exploration, moreover no studies focus on risk factors for cardiovascular morbidity. Herein we identified the risk factors for cardiovascular morbidity after pheochromocytoma surgery in Chinese patients. We retrospectively reviewed 262 patients who underwent unilateral surgical resection of pheochromocytoma at our center between 1 January 2007 and 31 December 2016. Patient demographics and extensive perioperative data were recorded and evaluated. Adjusted odds ratios and 95% confidence intervals were determined by multivariate logistic regression. Cut-off values and the area under the curve for continuous risk factors were calculated based on receiver operating characteristic curve analysis. A p-value <0.05 was considered statistically significant. Of the 262 patients, 63 (24.0%) had cardiovascular morbidity. The independent risk factors for cardiovascular morbidity were low body mass index, large radiographic tumor size, coronary heart disease, no preoperative crystal/colloid administration, and intraoperative hemodynamic instability; the corresponding odds ratio were 0.762 (p < 0.001), 1.208 (p = 0.010), 2.378 (p = 0.012), 2.720 (p = 0.011), and 4.764 (p = 0.001), respectively. The optimal cut-off values for body mass index and radiographic tumor size were 24.59 kg/m² and 6.05 cm. We found that cardiovascular morbidity is common in patients after pheochromocytoma surgery. We identified five independent risk factors for cardiovascular morbidity. Identification of these risk factors may help to improve treatment strategies.

Key words: Pheochromocytoma, Morbidity, Intraoperative hemodynamic instability

PHEOCHROMOCYTOMA is a rare, neuroendocrine tumor that originates from the chromaffin cells of the adrenal medulla [1]. The incidence of pheochromocytoma is 0.2–0.8/100,000 persons per year, and pheochromocytomas co-exist in 0.1%–1% of patients with hypertension and 5% of patients with adrenal incidentaloma [2]. Large amounts of catecholamines, such as epinephrine, norepinephrine, and dopamine, are synthesized and secreted by pheochromocytomas, which cause a constellation of clinical symptoms, including hypertension, headache, palpitations, perspiration, and other cardiovascular manifestations.

Surgical resection is the primary treatment strategy for pheochromocytoma [3], however, surgical resection carries a high risk of perioperative morbidity and mortality. Indeed, it has been reported that the mortality rate can be as high as 50% in patients undergoing surgical resection of a pheochromocytoma, but widespread improvements in preoperative medical preparation, anesthesia, and surgical techniques have significantly reduced the mortality rate to 0%–2.9% [1]. Severe morbidity, especially cardiovascular morbidity, is still common, difficult to manage, and the associated risk factors have not been established [4].

Previous studies have reported that some risk factors of intraoperative hemodynamic instability, such as tumor size, surgical approach, and catecholamine levels, which may be closely correlated with morbidity after surgical resection of pheochromocytoma, [5, 6]; the results from previous studies have been inconsistent. Furthermore, no studies have investigated the risk factors associated with cardiovascular morbidity, which are more closely related to pheochromocytoma surgery in Chinese. Therefore, we aimed to identify the risk factors for cardiovascular morbidity following surgical resection of pheochromocytomas in a large cohort of Chinese patients.
Methods

Patients

We retrospectively studied 302 patients who underwent surgical resection of pheochromocytomas at our center between 1 January 2007 and 31 December 2016. Forty patients were excluded from the study because of ectopic pheochromocytomas and missing data. In total, 262 patients were included in the final analysis (Fig. 1). Ethical approval (Ethical Committee No. 2018PS398K) was provided by the Institutional Research and Ethics Committee of the Shengjing Hospital Affiliated China Medical University in Shenyang, China. Informed consent from all eligible patients was obtained.

Inclusion and exclusion criteria

The diagnosis of a pheochromocytoma was confirmed by pathologic examination and patients who underwent unilateral laparoscopic or open adrenalectomy were included. Clinical stage was localized (apparently benign) disease and American Society of Anesthesiologists (ASA) score was 1–3. Patients converted to laparotomy and those who underwent bilateral adrenalectomy or surgery for ectopic pheochromocytoma were excluded.

Intervention

In our institution, some patients who had typical biochemical and radiographic manifestations of pheochromocytoma were treated with doxazosin, terazosin, or prazosin for at least 2 weeks preoperatively. A beta-adrenergic blocker was added to control tachycardia if necessary. Subsequently, oral hydration was encouraged and some patients who had malignant hypertension or large tumors were admitted for intravenous crystalloid and colloid (2,000 mL/day) fluid resuscitation or blood transfusion 2–3 days before surgery. Exceptions to this approach included patients who had normal blood pressure and biochemical testing and an atypical radiographic manifestation of a pheochromocytoma. The criteria of adequate preoperative medical preparation included blood pressure <130/80 mm Hg, heart rate <90/min, and hematocrit <0.45. Patients were administered general anesthesia and all surgical procedures were performed by qualified surgeons and anesthesiologists with extensive clinical experience.

Outcomes

Patient demographics (gender, age, and BMI), comorbidity (ASA score, diabetes mellitus, coronary heart disease [CHD], hypertension, and arrhythmias), disease characteristics (tumor sidedness and size, tumor necrosis, and enhanced computed tomography difference), extensive preoperative data (use of an alpha-adrenoreceptor antagonist, use of crystalloid or colloid fluids, blood transfusion, and 24-hour urine vanillylmandelic acid level), intraoperative data (surgical approach, duration of surgery, intra-operative hemodynamic [IHD] instability, and blood loss), and postoperative data (use of glucocorticoids and morbidity) were recorded and compared.

Data on cardiovascular morbidity were collected and classified according to the Clavien-Dindo classification [7], with Clavien I indicating mild morbidity and Clavien II and above indicating severe morbidity. Cardiovascular morbidity was defined as complications related to the cardiovascular system, such as prolonged postoperative hypotension requiring norepinephrine, the need for blood transfusion, myocardial ischemia, stroke, ventricular fibrillation, and pulmonary embolism or deep vein thrombosis. The definition of IHD instability was the presence of at least one intraoperative systolic blood pressure (SBP) >200 mm Hg, a mean arterial pressure (MAP) <60 mm Hg, or the requirement for norepinephrine or blood transfusion to maintain normal intraoperative blood pressure [8].

Statistical analysis

Data were analyzed using SPSS 22.0 for Windows (SPSS Inc., Chicago, IL, USA). The normality of continuous variables was determined using the Shapiro-Wilk test. Normally distributed continuous variables were presented as the mean ± standard deviation (SD); non-normally continuous variables were presented as the median (interquartile range). The means of two continuous normally distributed variables were compared by an independent samples Student’s t-test. The Mann-Whitney U test was used to compare two continuous non-normally distributed variables. Categorical variables were reported as a number (percentage). The chi-squared and Fisher’s
exact tests was used for comparison of categorical variables. Baseline variables that were considered clinically relevant or that had a $p$-value <0.1 based on univariate analysis were included in a multivariate binary logistic regression model. Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were also determined after adjusting for potential confounders by binary logistic regression. Cut-off values and the area under the curve (AUC) for continuous variables, which were independent risk factors for morbidity, were calculated through receiver operating characteristic (ROC) curve analysis. A two-tailed $p$-value <0.05 was considered statistically significant.

Results

Among the 262 patients, the mean age was 52.2 years, with an equal number of males and females. Seventy-eight patients (29.8%) had severe postoperative morbidity (Clavien II and above) and 93 (35.5%) had mild morbidity (Clavien I) who recovered promptly with anti-pyretics, analgesics, or electrolytes. The details of the patient demographics and perioperative data are shown in Table 1.

There were 63 patients (24.0%) with cardiovascular related morbidity. In all, 52 (19.4%) patients with Clavien II morbidity had prolonged hypotensive episodes requiring norepinephrine or blood transfusion to maintain normal blood pressure. There were 4 patients (1.5%) with Clavien III morbidity unrelated to the cardiovascular system who required surgical intervention. Fourteen patients had Clavien IV morbidity, 8 of which were cardiovascular related, including myocardial infarction, stroke, ventriculart fibrillation, and pulmonary embolism or deep vein thrombosis. Four patients (1.5%) with Clavien V morbidity died during the perioperative period. The details of these are shown in Table 2.

Patients with cardiovascular morbidity had lower BMI (21.9 vs. 24.1 kg/m², $p < 0.001$) and larger radiographic tumor sizes (6.6 vs. 5.2 cm, $p < 0.001$) compared with patients without cardiovascular morbidity. A higher proportion of females (68.3% vs. 45.2%, $p = 0.001$), CHD (47.6% vs. 30.7%, $p = 0.014$), tumor necrosis (49.2% vs. 32.7%, $p = 0.018$), no administration of crystalloid and colloid preoperatively for volume expansion (58.7% vs. 44.7%, $p = 0.052$), IHD instability (87.3% vs. 55.8%, $p < 0.001$), and use of glucocorticoids postoperatively (50.8% vs. 46.2%, $p = 0.054$) were noted in patients with cardiovascular morbidity compared to patients without cardiovascular morbidity. All of these variables were significant based on the univariate analysis and were then included in the multivariate analysis (Table 3).

There were five independent risk factors for cardiovascular morbidity in patients undergoing surgical resection of pheochromocytoma based on multivariate binary logistic regression: lower BMI (OR = 0.762, $p < 0.001$), larger radiographic tumor size (OR = 1.208, $p = 0.010$), CHD (OR = 2.378, $p = 0.012$), no administration of crystalloid or colloid preoperatively for volume expansion (OR = 2.720, $p = 0.011$), and IHD (OR = 4.764, $p = 0.001$) (Table 4).

In addition, the optimal cut-off points for BMI and radiographic tumor size were 24.25 kg/m² and 6.05 cm, respectively, based on ROC curve analysis (Fig. 2). We transformed BMI and tumor size continuous variables into categorical variables based on the cut-off points; the ORs of BMI (lower vs. higher) and tumor size (larger vs. smaller) were 4.858 ($p < 0.001$) and 2.434 ($p = 0.025$), respectively.

Discussion

Surgical resection is the preferred strategy for pheochromocytoma treatment, but surgical resection carries a high risk of morbidity during the perioperative period, even though preoperative medical preparation, anesthesia, and surgical techniques have improved greatly in recent years [9]. Establishing the risk factors for pheochromocytoma morbidity will lead to better treatment outcomes. Indeed, cardiovascular risk factors are the most common causes of morbidity in patients after pheochromocytoma surgery. Unfortunately, there are few retrospective, small-size studies on this issue in the literature and risk factors remain unclear, especially among the Chinese population. We therefore conducted this study in a large group of patients from a single center in China.

In our cohort, the mean age was 52.2 years, which is nearly 10 years older than Caucasian patients in whom the peak incidence of pheochromocytoma occurs in the 30 to 40 year age group and the average age at diagnosis is 43.9 years [10]. The incidence of pheochromocytoma in the current study cohort was equal between males and females, as in Caucasian patients.

The Clavien classification was used for evaluating pheochromocytoma complications, with a focus on cardiovascular morbidity. In the current study, 78 (29.8%) patients had severe morbidity, which was slightly higher than prior reports in which the morbidity ranged from 0% to 20% [11]. Most morbidity (24.0%) were related to the cardiovascular system. In a retrospective study, Shen et al. [11] reported cardiovascular complications in 22% of 102 patients, which was the same as our results. Of patients with Clavien II morbidity, 19.8% had prolonged hypotensive episodes and required norepinephrine or blood transfusion to maintain a normal blood pressure,
which was higher than previous studies [11].

In this study, patients with a low BMI, CHD, large tumor size, no administration of crystal and colloid fluid preoperatively for volume expansion, and IHD were independent risk factors for cardiovascular morbidity.

A low BMI has not been previously reported as a risk factor in patients undergoing surgical resection of pheochromocytoma. We suggest that patients with a low BMI have a less effective circulatory volume as a result of a lower weight. Moreover, patients with a low BMI have peripheral vasoconstriction induced by catecholamines preoperatively, which results in increased intraoperative blood pressure fluctuation requiring vasoactive agents, volume expansion, or blood transfusion. The cut-off value for BMI was 24.59 kg/m² with an OR of 4.858.

Usually, patients with pheochromocytoma have a higher incidence of cardiovascular disease than patients with essential hypertension [12]. This study showed that CHD was also a significant risk factor for cardiovascular morbidity because prolonged exposure to elevated levels of catecholamines on the myocardium and coronary arteries leads to collagen deposition and fibrosis in the

### Table 1  Demographics and perioperative data of patients in this cohort

| Variable                                      | All patients (%) |
|-----------------------------------------------|------------------|
| Number of patients (%)                        | 262 (100)        |
| **Demographic characteristics**               |                  |
| Mean age (years)                              | 52.2 ± 12.5      |
| Sex (male/female)                             | 129 (49.2)/133 (50.8) |
| BMI (kg/m²)                                   | 23.6 ± 3.5       |
| **Comorbidities**                             |                  |
| ASA score 1/2/3                               | 62 (23.7)/175 (66.8)/25 (9.5) |
| Diabetes mellitus                             | 79 (30.2)        |
| Coronary heart disease                        | 91 (34.7)        |
| Hypertension normal vs. intermittent vs. continuous | 103 (39.3)/60 (22.9)/99 (37.8) |
| Arrhythmia                                    | 15 (5.7)         |
| **Preoperative data**                         |                  |
| Tumor side (left/right)                       | 128 (48.9)/134 (51.1) |
| Radiographic tumor size (cm)                  | 5.6 ± 2.6        |
| Tumor necrosis presented in CT or pathology   | 96 (36.6)        |
| Tumor enhanced CT difference value (Hu)       | 43.8 ± 20.5      |
| Use of alpha adrenoreceptor antagonists        | 141 (53.8)       |
| Use of crystal/colloid for volume expansion   | 136 (51.9)       |
| Use of blood transfusion                      | 66 (25.2)        |
| 24-hour urine VMA/normal upper limit value    | 1.4 (0.9–2.2)    |
| **Intraoperative data**                       |                  |
| Laparoscopy vs. open                          | 141(53.8)/121(46.2) |
| Duration of surgery (minutes)                 | 155.8 ± 68.7     |
| IHD                                           | 166 (63.4)       |
| Estimated blood loss (mL)                     | 200 (100–400)    |
| **Postoperative data**                        |                  |
| Use of glucocorticoids                        | 124 (47.3)       |

Continuous variables with normal distribution were reported as the mean ± standard deviation (SD); non-normal continuous variables were expressed as the median (interquartile range); categorical variables were reported as a number (percentage). BMI, body mass index; ASA, American Society of Anesthesiologists; CT, computed tomography; VMA, vanillylmandelic acid; IHD, intra-operative hemodynamic instability.
myocardium [12]. In a previous study, investigators also found that acute left cardiac dysfunction due to chronically elevated epinephrine was the basis for hypotension and circulatory failure after resection of a pheochromocytoma [13]. In our study, all four of the patients who died had CHD and died of prolonged postoperative hypotension induced multi-organ dysfunction.

Large pheochromocytoma size have a more prominent network of vessels and associated more blood loss during surgery [14, 15]. Meanwhile, large pheochromocytoma cause higher levels of catecholamine secretion accompanied by severe hypertension [14, 15], and higher blood pressure leads to increased bleeding during resection. Our study suggested that large tumor size is an independent risk factor for cardiovascular morbidity; the cut-off value for the tumor diameter was 6.05 cm. Natkaniec et

| Table 2 Cardiovascular morbidity of pheochromocytoma surgery |
|-----------------------------------------------|
| Complications                                      | Number 262 (100%) |
| Cardiovascular morbidity causes                   | 63 (24.0%) |
| Blood transfusion                                 | 23 (8.8%) |
| Prolonged hypotension                             | 29 (11.1%) |
| Myocardial infarction                             | 3 (1.1%) |
| Stroke                                           | 2 (0.8%) |
| Ventricular fibrillation/flutter                  | 1 (0.4%) |
| Pulmonary embolism/deep vein thrombosis           | 1 (0.4%) |
| Postoperative in-hospital mortality               | 4 (1.5%) |
| Clavien I                                         | 93 (35.5%) |
| Abdominal pain                                    | 36 (13.6%) |
| Hyperthermia                                      | 30 (11.5%) |
| Poor wound healing                                | 2 (0.8%) |
| Electrolyte disturbance/hypoproteinemia           | 20 (7.6%) |
| Nausea and vomiting                               | 2 (0.8%) |
| Abdominal distension                              | 3 (1.2%) |
| Clavien II                                        | 56 (21.4%) |
| Postoperative prolonged hypotension               | 29 (11.0%) |
| Blood transfusion                                 | 23 (8.8%) |
| Delirium                                          | 1 (0.4%) |
| Arrhythmia                                        | 2 (0.8%) |
| Pneumonia                                         | 1 (0.4%) |
| Clavien III                                       | 4 (1.5%) |
| Hydrothorax (thoracocentesis)                     | 3 (1.1%) |
| Hemorrhage (open laparotomy)                      | 1 (0.4%) |
| Clavien IV                                        | 14 (5.3%) |
| Myocardial infarction                             | 4 (1.6%) |
| Respiratory function failure                      | 6 (2.1%) |
| Pulmonary embolism/deep vein thrombosis           | 1 (0.4%) |
| Stroke                                           | 2 (0.8%) |
| Ventricular fibrillation/flutter                  | 1 (0.4%) |
| Clavien V                                         | 4 (1.5%) |
| Mortality                                         | 4 (1.5%) |

Categorical variables are reported as a number (percentage).
al. [16] also reported that intraoperative blood loss is significantly greater in patients with tumor diameters ≥6 cm based on 530 patients who underwent laparoscopic adrenalectomy. Agrusa et al. [17] and others [18], however, reported that tumor size does not correlate with blood loss. One of the reasons for the discrepancy may be that most of these patients had various adrenal tumors, whereas our study focused on patients with pheochromocytoma only.

Another independent risk factor for cardiovascular morbidity involved not infusing crystalloids or colloids for volume expansion. It was confirmed that exposure to fluctuating levels of circulating catecholamines during surgery may lead to a hypertensive crisis and prolonged hypotension; preoperative medical preparation is important to minimize this issue [19, 20]. All patients with pheochromocytoma should receive preoperative medical preparation and volume expansion to block the effects of

Table 3  Univariate analysis of cardiovascular morbidity

|                                       | Without morbidity | With morbidity | t/z/χ² | p-value |
|---------------------------------------|-------------------|----------------|--------|---------|
| Number of patients (%)               | 199 (76.0)        | 63 (24.0)      |        |         |
| **Demographic characteristics**       |                   |                |        |         |
| Mean age (years)                      | 51.6 ± 12.1       | 54.3 ± 13.6    | −1.521 | 0.129   |
| Sex (male/female)                     | 109 (54.8)/90 (45.2) | 20 (31.7)/43 (68.3) | 10.152 | 0.001   |
| BMI (kg/m²)                           | 24.1 ± 3.6        | 21.9 ± 2.7     | 4.611  | <0.001  |
| ASA score 1/2/3                       | 49 (24.6)/131 (65.8)/19 (9.5) | 13 (20.6)/44 (69.8)/6 (9.5) | 0.437 | 0.804   |
| **Comorbidity**                       |                   |                |        |         |
| Diabetes mellitus                     | 58 (29.1)         | 21 (33.3)      | 0.398  | 0.528   |
| Coronary heart disease                | 61 (30.7)         | 30 (47.6)      | 6.076  | 0.014   |
| Hypertension Normal vs. Intermittent vs. Continuous | 78 (39.2)/45 (22.6)/76 (38.2) | 25 (39.7)/15 (23.8)/23 (36.5) | 0.069 | 0.966   |
| Arrhythmia                            | 11 (5.5)          | 4 (6.3)        | 0.762  |         |
| **Preoperative data**                 |                   |                |        |         |
| Tumor side (left/right)               | 96 (48.2)/103 (51.8) | 32 (50.8)/31 (49.2) | 0.125 | 0.724   |
| Radiographic tumor size (cm)          | 5.2 ± 2.5         | 6.6 ± 2.9      | −3.547 | <0.001  |
| Tumor necrosis                        | 65 (32.7)         | 31 (49.2)      | 5.641  | 0.018   |
| Tumor enhanced CT difference (Hu)     | 43.2 ± 20.6       | 45.6 ± 20.2    | −0.782 | 0.435   |
| Use of α adrenoreceptor antagonists    | 106 (53.3)        | 35 (55.6)      | 0.101  | 0.751   |
| Without use of crystalloid and colloid| 89 (44.7)         | 37 (58.7)      | 3.761  | 0.052   |
| Use of blood transfusion              | 52 (26.1)         | 14 (22.2)      | 0.388  | 0.533   |
| 24-hour urine VMA/normal upper limit  | 1.4 (0.9–2.2)     | 1.36 (0.9–2.3) | −0.947 | 0.347*  |
| **Intraoperative data**               |                   |                |        |         |
| Laparoscopy vs. Open                  | 105 (52.8)/94 (47.2) | 36 (57.1)/27 (42.9) | 0.369 | 0.543   |
| Duration of surgery (minutes)         | 153.1 ± 70.1      | 164 ± 63.8     | −1.108 | 0.269   |
| IHD                                   | 111 (55.8)        | 55 (87.3)      | 20.482 | <0.001  |
| Estimated blood loss (mL)             | 200 (100–400)     | 200 (100–500)  | −1.218 | 0.223*  |
| **Postoperative data**                |                   |                |        |         |
| Use of glucocorticoids                | 92 (46.2)         | 32 (50.8)      | 0.400  | 0.054   |

Continuous variables with a normal distribution are reported as the mean ± standard deviation (SD); non-normal continuous variables are expressed as the median (interquartile range); categorical variables are reported as a number (percentage). An independent sample Student’s t-test was used to compare the means of two continuous normally distributed variables and the Mann-Whitney U test was used to compare the means of two continuous non-normally distributed variables. The chi-squared test or Fisher’s exact test was used for categorical variables.

* Mann-Whitney U test, † Fisher’s exact test
BMI, body mass index; ASA, American Society of Anesthesiologists; CT, computed tomography; VMA, vanillylmandelic acid; IHD intraoperative hemodynamic instability
released catecholamines and prevent large fluctuation of blood pressure [21]. Our study showed that intravenous infusion of crystalloid or colloid for volume expansion lowered the incidence of cardiovascular morbidity; however, the use of alpha-adrenergic receptor blockers and blood transfusion were not shown to be risk factors. Nevertheless, we should be aware that aggressive volume expansion may increase the workload on the heart [19, 20, 22], which may lead to heart failure. In contrast to our research results, a prospective study reported that preoperative fluid therapy had no impact on post-resection hypotension [23], which may reflect different volume expansion strategies.

The definitions of IHD instability are various. We defined IHD instability as the presence of at least one intraoperative SBP >200 mm Hg associated with a MAP <60 mm Hg or requiring norepinephrine or blood transfusion to maintain a normal intraoperative blood pressure. IHD instability remains a common complication during surgical resection of pheochromocytomas, despite adequate preoperative preparation [24]. Previous reports have shown that IHD instability occurs in 39%–48% of patients with pheochromocytomas [25, 26]. In our study, the incidence of IHD instability was 63.4%, which is higher than reported in Caucasians [27]. IHD instability is still the most important intraoperative and anesthetic challenge during pheochromocytoma resection, and has been proven to be an independent risk factor for morbidity [8], which is in agreement with our results. Hypertensive episodes occur most often during intubation and

Table 4 Multivariate binary logistic regression of cardiovascular morbidity

| Variable                              | OR   | 95% CI         | p    |
|---------------------------------------|------|----------------|------|
| Sex (female/male)                     | 1.892| 0.957–3.741    | 0.068|
| BMI (kg/m²)                           | 0.762| 0.670–0.867    | <0.001|
| BMI (lower vs. higher)¹                | 4.858| 2.083–11.330   | <0.001|
| Coronary heart disease                | 2.378| 1.205–4.691    | 0.012|
| Radiographic tumor size (cm)          | 1.208| 1.047–1.394    | 0.010|
| Radiographic tumor size (larger vs. smaller)¹ | 2.434| 1.118–5.298    | 0.025|
| Tumor necrosis presented in CT or pathology | 1.002| 0.984–1.021    | 0.805|
| Whitout use of crystal/colloid preoperatively | 2.720| 1.256–5.894    | 0.011|
| IHD                                   | 4.764| 1.884–12.050   | 0.001|
| Use of glucocorticoids postoperatively | 1.532| 0.719–3.267    | 0.269|

¹ The optimal cut-off points for BMI and radiographic tumor size were 24.25 kg/m² and 6.05 cm, respectively, based on ROC curve analysis. We transformed BMI and tumor size continuous variables into categorical variables based on the cut-off points.

OR, odds ratio; CI, confidence interval; BMI, body mass index; IHD, intraoperative hemodynamic instability

Fig. 2 ROC curve continuous independent risk factors of cardiovascular morbidity.

A. BMI in cardiovascular morbidity. B. Tumor size in cardiovascular morbidity.

ROC, receiver operating characteristic curve; AUC, area under the curve; BMI, body mass index
separation of the tumor; hypotensive episodes often occur after resection of the pheochromocytoma [28]. Continuous invasive arterial blood pressure monitoring and vasoactive agent administration by an experienced anesthesia team are necessary to avoid hemodynamic instability [29]. When the main adrenal vein is ligated, anti-hypertensive drugs are discontinued and vasoconstrictors are prepared [14]. Hemodynamic changes should be strictly monitored during the first 24–48 h after tumor removal [22] and intensive care is required throughout the perioperative period to optimize outcomes.

There were several limitations to this study. First, this was a retrospective study with select data from one center and was therefore subject to the weaknesses of this approach. Second, because there are various perioperative strategies for management which were not standardized, these differences could have influenced the final results, such that we were unable to include dosage and duration of preoperative management in the analysis. A multicenter randomized trial with standardization of preoperative management, intraoperative anesthetic management, and operative approach is required to confirm these independent risk factors.

Conclusions

This large retrospective study in a single center confirmed that cardiovascular morbidity is common in patients after surgical resection of pheochromocytomas. We identified the following five independent risk factors for cardiovascular morbidity: low BMI; large radiographic tumor size; CHD; no administration of crystalloid or colloids preoperatively for volume expansion; and IHD. Identification of these risk factors may help to improve perioperative strategies for patients with pheochromocytoma; however, randomized controlled trials are warranted to confirm the predictive value of these variables and to investigate the precise mechanisms underlying the correlation.

Author Contributions

Ning Wen had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Ning Wen.

Acquisition of data, analysis and interpretation of data: Song Bai, Zichuan Yao and Xianqing Zhu.

Drafting of the manuscript and critical revision of the manuscript for important intellectual content: Song Bai.

Statistical analysis: Rongzhi Wang, Zidong Li.

Obtaining funding and other (figures): Song Bai, Zidong Li, Yuzhong Jiang.

Conflicts of Interests

The authors declare that they have no competing interests.

Financial Disclosures

Bin Wu certifies that all conflicts of interest, including specific financial interests, relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (e.g., employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: None.

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Disclosure

None.

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