# Surgical Outcomes in the Pheochromocytoma Surgery. Results From the PHEO-RISK STUDY.

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# Abstract

**Purpose:** To identify presurgical and surgical risk factors for postsurgical complications in the pheochromocytoma surgery.

**Methods:** A retrospective study of pheochromocytomas submitted to surgery in ten Spanish hospitals between 2011 and 2021. Postoperative complications were classified according to Clavien-Dindo scale.

**Results**: One hundred and sixty-two surgeries (159 patients) were included. Preoperative antihypertensive blockade was performed in 95.1% of the patients, being doxazosin in monotherapy (43.8%) the most frequent regimen. Patients pre-treated with doxazosin required intraoperative hypotensive treatment more frequently (49.4% vs 25.0%, P=0.003) than patients treated with phenoxybenzamine, but no differences in the rate of intraoperative and postsurgical complications were observed. However, patients treated with phenoxybenzamine had a longer hospital stay (12.2±11.16 vs 6.2±6.82, P<0.001) than those treated with doxazosin. Hypertension resolution was observed in 78.7% and biochemical cure in 96.6% of the patients. Thirty-one patients (19.1%) had postsurgical complications. Prolonged hypotension was the most common, in 9.9% (n=16), followed by hypoglycaemia in 6 patients and acute renal failure in 4 patients. 13.0% of complications had a score ≥3 in the Clavien-Dindo scale. Postsurgical complications were more common in in patients with diabetes, cerebrovascular disease, higher plasma glucose levels, higher urinary free metanephrine and norepinephrine, and with pheochromocytomas larger than 5 cm.

**Conclusion:** Preoperative medical treatment and postsurgical monitoring of pheochromocytoma should be especially careful in patients with diabetes, cerebrovascular disease, higher levels of plasma glucose and urine free metanephrine and norepinephrine, and with pheochromocytomas >5 cm, due to the higher risk of postsurgical complications.


# Introduction:

Pheochromocytomas are rare neuroendocrine tumours that produce catecholamines [1]. They are a life-threatening condition because catecholamine secretion is unpredictable, resulting in hypertension, arrhythmia, and/or other cardiovascular complications [2]. Surgery represents the primary treatment for pheochromocytomas [1]. Due to improvements in perioperative treatment, anaesthesia and surgical techniques, the mortality has dropped markedly in the last thirty years, but the risk of cardiovascular complications remains still high [3]. Intraoperative complications, including hypertensive crisis, hemodynamic instability and tachyarrhythmias, among others, have been reported in 30–50% of the pheochromocytoma surgeries [4][5][6]. The main postoperative major complications are prolonged hypotension and rebound hypoglycaemia [1]. However, postsurgical complications are usually less reported in pheochromocytoma studies, and are usually described in around 20–30% of the patients in recent series [4][7][8][9].Few studies have evaluated the grade of these complications using validate scales as the Clavien-Dindo score [4][10][9][8]. Moreover, studies evaluating risk factors for postsurgical complications are even more scarce and findings are generally heterogeneous [4][7][11][12]. The reported

risk factors for postsurgical complications included diabetes [4], tumour size [11], preoperative total urinary metanephrine excretion [7], preoperative systolic blood pressure [7] and open adrenalectomy [12], among others.

The aim of our study was to analyse the relation between presurgical patient´s and tumour phenotype and the type of preoperative and surgical management with the risk of postsurgical complications based on the Clavien-Dindo classification in a large cohort of patients with pheochromocytomas consecutively operated in ten tertiary Spanish hospitals between 2011 and 2020 (PHEO-RISK Study).

## Methods:

# Study design

A retrospective study of patients who underwent adrenalectomy for pheochromocytoma between 2011–2020 in ten tertiary hospitals was carried out. Inclusion criteria were patients with confirmed histological diagnosis of pheochromocytoma with available clinical, biochemical, radiological and presurgical, intraoperative and surgical management information. Only patients without evidence of metastatic disease before surgery were included. A total of 162 consecutive adrenalectomies performed in 159 patients were included. Patients were identified through a systematic electronic search in the Pathology and Admission Departments files of the different hospitals. The study was approved by the Ethics Committee of Hospital Universitario Ramón y Cajal on 22th April 2021, ACTA 411)

# Data collection and clinical definitions

Data were extracted from the electronic medical records system of the different hospitals and were collected in an electronic database (RedCAP® database). Information registered in the database included demographic, clinical, biochemical, hormonal and radiological data, anesthetic risk (American Society of Anesthesiologists classification (ASA)), and variables related to preoperative, intraoperative, and surgical management. Hormonal studies included urinary catecholamines (norepinephrine, epinephrine, and dopamine) and urinary and/or plasma free metanephrines (metanephrine and normetanephrine).

Registered intraoperative complications included intraoperative hypertensive crisis, intraoperative bleeding, prolonged hypotensive episode, arrhythmias, hemodynamic instability, and others. Postoperative complications were classified in hypertensive crisis, hypotension episode, hypoglycaemia, acute renal failure, postsurgical ileus and others. They were also classified based on their severity, following the classical Clavien-Dindo scale, considering any deviation from the normal postoperative course which required pharmacological treatment or interventional procedures, i.e., grade II or higher on the Clavien-Dindo classification [13]. Postoperative hypertensive crisis was defined as a systolic BP (SBP) ≥ 180 mm Hg or diastolic BP (DBP) ≥ 110 mm Hg; postsurgical hypotensive episode as SBP < 90 mmHg and/or DBP < 60 mmHg associated with typical clinical symptoms of low BP; hypoglycaemia as a plasmatic or capillary glucose level < 70mg/dl associated with compatible clinical symptoms; and acute renal failure as a ≥ 0.3 mg/dL increase in serum creatinine within 48 hours [14].

# Surgical and anaesthetic management

The choice to operate laparoscopically or with an open approach was based on the malignancy risk of the patient and the tumour size. All surgeries were conducted under general anaesthesia. The choice of the anaesthetic agent, vasoactive and hypotensive drugs and other additional monitoring were left to the anaesthesiologist´s judgment. Patients were all sent to the intensive care unit postoperatively and transferred to the general ward after once hemodynamic variables were stable.

# Statistical analysis

The statistical analysis was performed using STATA.15. Normality assumption was checked using Shapiro-Wilk test. Categorical variables are expressed as percentages and absolute values and quantitative variables as mean ± standard deviation or median and ranges depending on the normal distribution of the variable. Odds ratios (OR) with 95% confidence intervals were calculated as association measures using logistic regression model. The chi2 test was performed for the comparison of categorical variables between independent groups and the t-test for comparison between means. In all cases, a two-tailed P value < 0.05 or a 95% confidence interval not including the number 1, were considered statistically significant.

## Results:

# General characteristics

The study population included 159 patients (75 men and 84 women, mean age at diagnosis: 51.6 ± 16.4 years) (Table 1). Genetic information was available in 136 patients, of whom 29.4% had a predisposing hereditary syndrome (the most common MEN2A). 162 surgeries were included (3 patients underwent adrenalectomy twice), laparoscopic adrenalectomy in 156 patients (bilateral in 12), open adrenalectomy in 14 (bilateral in 2 patients). After a median follow-up of 41.2 months, 6 patients died, but only one death was attributable to the pheochromocytoma (progression of metastatic disease).

Table 1
Baseline patient´s cohort characteristics (n = 159)

| PARAMETER | VALUE |
|---|---|
| CLINICAL | |
| Age (years) | 51.6 ± 16.4 |
| Female sex | 52.8% (n = 84) |
| Smoking (n = 156) | 25.6% (n = 40) |
| Diabetes | 25.8% (n = 41) |
| Hypertension | 60.4% (n = 96) |
| Dyslipidaemia | 34.0% (n = 54) |
| Obesity | 13.8% (n = 22) |
| Cerebrovascular disease | 4.4% (n = 7) |
| Cardiovascular disease | 13.8% (n = 22) |
| Left ventricular hypertrophy (n = 61) | 41.0% (n = 25) |
| Chronic kidney disease | 7.6% (n = 12) |
| Body mass index (kg/m$^2$) | 25.4 ± 5.37 |
| Systolic blood pressure (mmHg) | 128.5 (range 96–220) |
| Diastolic blood pressure (mmHg) | 80 (range 50–120) |
| ASA II | 40.2% (n = 51) |
| ASA III | 52.0% (n = 66) |
| BIOCHEMICAL AND RADIOLOGICAL | |
| Fasting plasma glucose (mg/dl) | 101 (range 69–272) |
| GFR (MDRD4) (ml/min/1.73m2) | 88.5 (range 36–116) |
| Total cholesterol (mg/dl) | 187 (range 112–311) |
| Triglycerides (mg/dl) | 91 (range 37–417) |
| Urinary free metanephrine levels | 921.3 (range 15-53475) |
| Urinary free normetanephrine | 1099.4 (range 26-19166) |
| Urinary epinephrine (µg/24h) | 36.7 (range 0.56–966) |
| Urinary norepinephrine | 130.4 (range 13-12942) |
| | 111.0 (range 2.5–2841) |
| GFR = glomerular filtration rate. | 648.0 (range 53-7171) |

| PARAMETER | VALUE |
| --- | --- |
| Plasma free metanephrine levels (µg/dl) | 40 (range 8-110) |
| Plasma free normetanephrine (µg/dl) | 5% (n = 8) |
| Tumour size (mm) | |
| Bilaterality | |

GFR = glomerular filtration rate.

# Preoperative and anaesthetic medical treatment

Preoperative antihypertensive blockade was performed in 95.1% of the patients, with doxazosin in monotherapy in 43.8% (n = 71) (median dose 6 mg/day (range 2-24mg/day), phenoxybenzamine in monotherapy in 24.1% (n = 39), (median dose 30 mg/day (range 5-120 mg/day), amlodipine in monotherapy in 2 patients and combined therapy in the rest (Table 2). Prolonged (≥ 14 days) preoperative alpha-adrenergic receptor blocker treatment had been given to 62.6% of the patients. Additional beta-adrenergic blockade was provided to 51.9% of the patients after a median interval of 9 days (range 1–90) before surgery. No difference was found in the proportion of patients achieving BP objectives (≤ 130/80 mmHg) between patients pre-treated with doxazosin (n = 89) vs phenoxybenzamine (n = 56) (76.1% vs 62.5%, P = 0.093). Neither in the needed of intraoperative vasoactive drugs (37.9 vs 26.4%, P = 0.162). However, those pre-treated with doxazosin required intraoperative hypotensive treatment more frequently than those pre-treated with phenoxybenzamine (49.4% vs 25.0%, P = 0.003). However, overall, there were no statistically significant differences in the occurrence of intraoperative (38.2% vs 23.2%, P = 0.060) and postsurgical (19.1% vs 23.2%, P = 0.552) complications between both groups, but patients treated with phenoxybenzamine had a longer hospital stay (12.2 ± 11.16 vs 6.2 ± 6.82, P < 0.001). No differences were observed in BP levels before medical and surgical treatment, nor in the rate of intraoperative complications between the different presurgical treatment regimens (P > 0.05).

Table 2
Presurgical antihypertensive regimens, blood pressure levels and intraoperative complications

| Pre-treatment regimen, % | Pre-treatment SBP/DBP | SBP/DBP before surgery | Intraoperative hypertensive crisis | Intraoperative hypotensive crisis | Hemodynamic instability |
|---|---|---|---|---|---|
| Doxazosin monotherapy (n = 71) | 133.3 ± 21.8/ 79.9 ± 12.9 | 117.8 ± 10.4/ 70.6 ± 10.4 | 15.5% (n = 11) | 16.9% (n = 12) | 11.3% (n = 8) |
| PHENO monotherapy (n = 39) | 128.7 ± 22.5/ 77.4 ± 14.2 | 113.1 ± 23.1/ 70.9 ± 10.6 | 18.0% (n = 7) | 18.0% (n = 7) | 7.7% (n = 3) |
| Doxazosin + PHENO (n = 5) | 123.0 ± 24.5/ 81.8 ± 19.8 | 120.0 ± 18.3/ 77.5 ± 9.6 | 80.0% (n = 4) | 40.0% (n = 2) | 20.0% (n = 1) |
| Doxazosin + amlodipine (n = 15) | 159.5 ± 31.0/ 94.3 ± 16.3 | 124.3 ± 18.2/ 71.5 ± 8.6 | 46.7% (n = 7) | 53.3% (n = 8) | 20.0% (n = 3) |
| PHENO + amlodipine (n = 6) | 144.3 ± 27.4/ 86.7 ± 17.9 | 122.0 ± 18.1/ 73.8 ± 7.2 | 33.3% (n = 2) | 33.3% (n = 6) | 16.7% (n = 1) |
| Other regimens (n = 24) | 139.5 ± 34.8/ 81.2 ± 19.8 | 122.0 ± 16.3/ 74.9 ± 9.8 | 45.5% (n = 10) | 40.9% (n = 9) | 27.3% (n = 6) |

PHENO = phenoxybenzamine, SBP/DBP = systolic blood pressure/diastolic blood pressure

# Surgical outcomes

Hypertension resolution was observed in 78.7% of the patients, and pheochromocytoma biochemical cure in 96.6%. Patients with hypertension resolution tended to need less antihypertensive drugs for blood pressure control than those who remained hypertensive after surgery (1.4 ± 0.97 vs 1.9 ± 1.18, P = 0.072). Postsurgical complications occurred in 31 patients (19.1%). Postoperative hypotension was the most common (Fig. 1). As expected, patients who had complications had a longer hospital length of stay (11.8 ± 11.72 vs 7.5 ± 8.29, P = 0.018). Among postsurgical complications, 53.3% had a score ≥ 2 in the Clavien-Dindo scale. Two patients had a score of 3 and 2 patients a score of 4. Postsurgical complications were more common in patients older than 65 years, patients with diabetes, with cerebrovascular disease, with higher levels of serum glucose or urinary metanephrine and norepinephrine, and with pheochromocytomas larger than 5 cm (Table 3). The higher risk of complications in elderly

patients was related to a higher prevalence of diabetes and cerebrovascular disease in these patients (adjusted OR = 1.68 [0.68–4.19], P = 0.262). Similarly, higher risk of complications in larger tumours disappeared after adjustment for urinary free metanephrine and norepinephrine levels (adjusted OR = 2.29 [0.59–8.85]).

Table 3
Risk factors for postsurgical complications

| Variable | OR [95% CI], p value |
|---|---|
| Female sex | OR = 1.48 [0.67–3.25], P = 0.326 |
| Age > 65 years | **OR = 2.43 [1.05–5.62], P = 0.042** |
| Diabetes | **OR = 3.17 [1.39–7.23] P = 0.007** |
| Hypertension | OR = 2.15 [0.90–5.15], P = 0.076 |
| Obesity | OR = 1.2 [0.49–2.95], P = 0.693 |
| Cardiovascular disease | OR = 0.93 [0.51–1.70], P = 0.800 |
| Cerebrovascular disease | **OR = 6.32 [1.34–29.88], P = 0.022** |
| BMI, kg/m2 | OR = 0.98 for each kg/m$^2$ [0.88–1.09] P = 0.720 |
| Presurgical BP > 130/80 | OR = 1.48 [0.60–3.69], P = 0.403 |
| Fasting plasma glucose | **OR = 1.13 for each 10mg/dl [1.03–1.25], P = 0.013** |
| Urinary free metanephrine (µg/24h) | **OR = 1.01 for each 100 mcg/24h [1.00-1.02], P = 0.010** |
| Urinary free normetanephrine (µg/24h) | OR = 1.01 for each 100 mcg/24h [1.00-1.03], P = 0.088 |
| Plasma free metanephrine levels (µg/dl) | OR = 1.00 for each 10 mcg/dl [0.98–1.01], P = 0.743 |
| Plasma free normetanephrine (µg/dl) | OR = 1.00 for each 10 mcg/dl [0.98–1.01], P = 0.279 |
| Urinary epinephrine (µg/24h) | OR = 1.20 for each 100 mcg/24h [0.95–1.50], P = 0.125 |
| Urinary norepinephrine (µg/24h) | **OR = 1.08 for each 100 mcg/24h [1.02–1.15], P < 0.001** |
| Tumour > 50 mm | **OR = 2.70 [1.21–6.02], P = 0.016** |
| Open adrenalectomy | OR = 1.79 [0.52–6.15], P = 0.370 |
| Doxazosin pre-treatment | OR = 0.78 [0.35–1.76], P = 0.554 |
| Beta-blockers | OR = 0.61 [0.28–1.35], P = 0.219 |
| Intraoperative complications | OR = 1.94 [0.87–4.33], P = 0.107 |

# Discussion:

In our study, 19.1% of the patients submitted to pheochromocytoma surgery experienced postsurgical complications, and 13% of them were classified as severe. Prolonged hypotension was the most common, occurring in 9.9% of the cases. Postsurgical complications were more common in elderly patients and patients with diabetes, a history of cerebrovascular disease, higher levels of plasma glucose and urinary free metanephrine and norepinephrine, and with pheochromocytomas larger than 5 cm.

The Clavien-Dindo classification was used for evaluating postoperative pheochromocytoma complications. The rate of postsurgical complications in our study was of 19.1%, but only 4 patients (13.0%) suffered from major complications (Clavien-Dindo ≥ 3). The rate of complications observed in our study is in accordance with other recent reported series from high-volume centres [7][8][9]. Several series also described prolonged hypotension as the most common postsurgical complications [15][7][16][17]. However, the rate of complications is widely variable among series, ranging from 10–40% [8][18][11][19]. There are several plausible explanations for this wide range, including referral biases, differences in the definition of complications and in the type of complications reported, and importantly, the decade of the performed research as it is known that a significant reduction in pheochromocytoma surgical treatment morbidity and mortality has taken place over recent decades [20]. In agreement with our study, series evaluating the severity of complications found similar figures of grade III and IV complications in the Clavien-Dindo score [10][9][11], although in some series severe complications occurred in up to 31% of the cases [8].

We found that postsurgical complications were more common in diabetic patients and in patients with cerebrovascular disease, as it has been previously described [8]. The higher risk for complications in elderly patients was related to the higher prevalence of these comorbidities. In line with our results, Srougi *et al.* [21] found that the mean Charlson score was 3.6 ± 1.3 in the older group and 0.89 ± 1.0 in the younger group, and elderly patients had a higher rate of postoperative complications (60% vs 18.9%, $p = 0.01$), but they did not adjusted the risk of complications for comorbidities as we did. Nevertheless, in a more recent study [22], the same authors included a larger number of patients, and they performed a multivariate analysis including age and comorbidities, observing that patients age ($p = 0.004$), comorbidities ($p = 0.003$) and pathological diagnosis ($p = 0.003$) were independent predictors of postoperative complications. In contrast with our results, a recent study comparing laparoscopic outcomes in elderly and young pheochromocytoma patients [23], did not find any difference in terms of haemodynamic changes during surgery and complications. However, this study included only 54 patients, and only two of them had experienced surgical complications, limiting the power of their results. No differences in hemodynamic instability, morbidity and mortality according to patient´s age [24][25][7][26][27][24] was reported in other studies either. So, based on results, although it is known that elderly patients usually have cardiovascular, pulmonary and hepatorenal changes that impact their response to anaesthesia, surgical stress and postoperative rehabilitation [28], the most important determinant of their higher risk of complications seems to be related to the association with higher rate of comorbidities in elderly, especially diabetes and cerebrovascular disease. Therefore, we suggest focusing on a strict control of comorbidities in elderly patients with pheochromocytoma undergoing surgery.

Other risk factor for postsurgical complications in our series was a higher level of urinary free metanephrine and norepinephrine, being urinary norepinephrine the most powerful biochemical predictor of complications. In accordance with our results, Namekawa *et al.* [16] showed that urinary epinephrine and norepinephrine were correlated with prolonged hypotension after tumour resection. Nevertheless, conflicting results have been described, some authors observed that urinary epinephrine (OR 1.18; 95% CI 1.04–1.35) and dopamine (OR 4.38; 95% CI 1.21–15.86), but not norepinephrine were independent risk factors for hypotension [17], and even some studies did not find any influence of the amount of catecholamines secretion and risk of postoperative hypotension [8][10].

We also observed that patients receiving selective alpha-blockade required intraoperative vasodilators more frequently than those treated with non-selective alpha-blockade. Similar results were reported in a recent systematic review and meta-analysis of 1344 patients [29], describing that intraoperative vasodilators were used more frequently in the group of selective alpha-blockade (OR: 2.46, 95% CI 1.44–4.20, P = 0.001). They also found a shorter length of hospital stay (WMD: -0.58 days, 95% CI: -1.12 to -0.04, P = 0.04) in patients treated with selective-alpha blockers, maybe the shorter stay could be related to the tendency to use phenoxybenzamine in hospitalized patients and use doxazosin on an outpatient basis. Supporting this finding, a recent randomized clinical trial comparing doxazosin and phenoxybenzamine [30] also described a need of higher number of vasodilating drug in the doxazosin group (P = 0.02). Nevertheless, they neither found differences in postoperative complications rate between both groups. The better control of intraoperative blood pressure, and the consequent lower need for vasodilators during surgery in the phenoxybenzamine group may be explained through its more effective inhibition of the α-adrenergic receptor, due to its non-competitive antagonism compared to the competitive binding provided by doxazosin [30].

Patients with tumours larger than 5 cm also had an increased risk of complications, but it was related to a greater functionality of the tumour. Tumour size is a well-known risk factor for postoperative [8][10][16][31][32][24] and intraoperative complications [11][24][27][33]. However, this relationship seemed to be due the real reason why size is associated with complications seemed to be related to a higher production of catecholamines in our study. In this line, Eisenhofer et al, [34] observed that tumour diameter showed strong positive relationships with 24-h urinary outputs of normetanephrine and metanephrine (r = 0.77; P < 0.001). Similar findings have been described by other authors [33], and also in other functioning adrenal tumours [35]. Besides, tumour size is a classical risk factor for recurrence [36] and malignancy [37]. Thus, tumour size should always be considered during the presurgical evaluation of pheochromocytoma and taken into account for a better planning of presurgical medical treatment and surgical approach.

Our study has certain limitations. First, it represents a retrospective review of data, which might incur recall bias. A second limitation is the likely variability of anaesthetic and surgical management between medical centres, The strengths of our study are the review of a large series of records from consecutive patients, with pheochromocytomas prepared for surgery in ten tertiary hospitals, and the precise definition of complications before data collection and analysis. Finally, a large sample of prospective randomized controlled studies is needed to further verify our conclusions.

# Conclusion:

Preoperative medical treatment and postsurgical monitoring of pheochromocytoma should be especially careful in patients with diabetes, cerebrovascular disease, higher levels of plasma glucose and urinary free metanephrine and norepinephrine, and with pheochromocytomas > 5 cm, due to the higher risk of postsurgical complications. Patients receiving selective alpha-blockade required intraoperative vasodilators more frequently than those treated with non-selective alpha-blockade, but no differences were observed in the rate of intraoperative and postsurgical complications.

# Declarations:

**Compliance with ethical standards:**

**Financial Support:** No financial support was received.

**Conflict of Interest:** The authors have no conflict of interest

**Ethical approval:** All procedures performed in the participants of the study were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

The study was approved by the Ethical committee of the Hospital Ramón y Cajal. Madrid. Spain (approval date: 22$^{th}$ April 2021, ACTA 411)

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# Figures

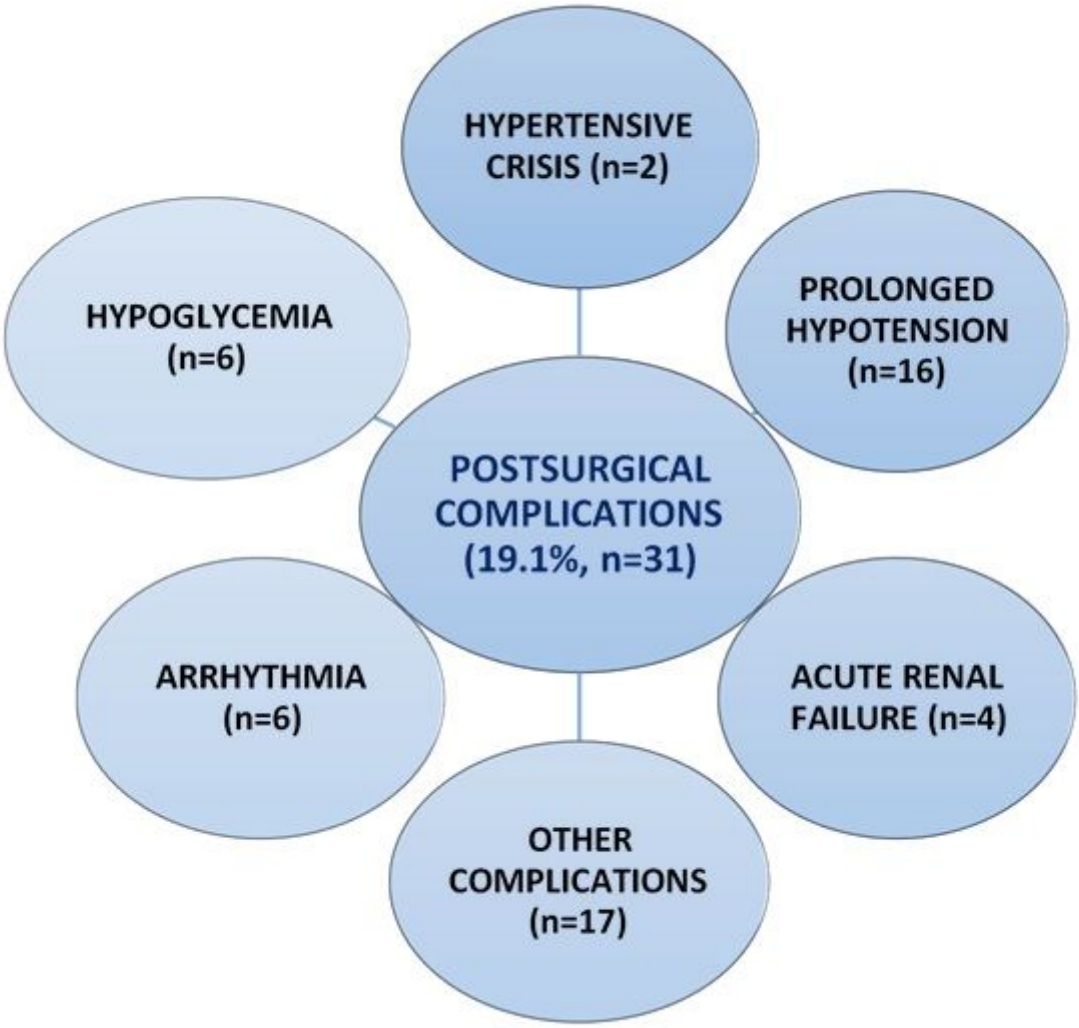


**Figure 1**

Postsurgical complications in the pheochromocytoma surgery