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Predictive factors for postoperative morbidity after laparoscopic adrenalectomy for pheochromocytoma: a multicenter retrospective analysis in 225 patients

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Abstract
Background Since the 1950s, preoperative medical preparation has been widely applied in patients with pheochromocytoma to improve intraoperative hemodynamic instability and postoperative complications. However, advancements in preoperative imaging, laparoscopic surgical techniques, and anesthesia have considerably improved management in patients with pheochromocytoma. In consequence, there is no validated consensus on current predictive factors for postoperative morbidity. The aim of this study was to determine perioperative factors which are predictive for postoperative morbidity in patients undergoing laparoscopic adrenalectomy for pheochromocytoma.
Study design It is a retrospective analysis of prospectively maintained databases in five medical centers from 2002 to 2013. Inclusion criteria were consecutive patients who underwent non-converted laparoscopic unilateral total adrenalectomy for pheochromocytoma.
Results Two-hundred and twenty-five patients were included. All-cause and cardiovascular postoperative morbidity rates were 16 % ($n = 36$) and 4.8 % ($n = 11$), respectively. Preinduction blood pressure normalization after preoperative medical preparation had no impact on postoperative morbidity. However, past medical history of coronary artery disease (OR [CI95 %] = 3.39; [1.317–8.727]) and incidence of intraoperative hemodynamic instability episodes (both SBP $\geq$ 160 mmHg and MAP $<$ 60 mmHg) (OR [CI95 %] = 3.092; [1.451–6.587]) remained independent predictors for postoperative all-cause morbidity. Similarly, past medical history of coronary artery disease (OR [CI95 %] = 14.41; [3.119–66.57]), female sex (OR [CI95 %] = 12.05; [1.807–80.31]), and incidence of intraoperative hemodynamic instability episodes (both SBP $\geq$ 200 mmHg and MAP $<$ 60 mmHg) (OR [CI95 %] = 4.13; [1.009–16.90]) remained independent predictors for postoperative cardiovascular morbidity.

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Conclusions This study identifies risk factors for cardiovascular and all-cause postoperative morbidity after laparoscopic adrenalectomy in current clinical setting. These data can help physicians to guide intra-operative blood pressure management and have to be taken into account in further studies.

Keywords Pheochromocytoma · Adrenalectomy · Hemodynamics · Blood pressure · Morbidity · Risk factors

Pheochromocytoma is a rare neuroendocrine tumor leading to excessive catecholamine release. Surgical therapy is the mainstay in the management of this disease, and current trends in minimally invasive surgery have provided technical advances that have improved patients' postoperative recovery and pain [1]. This evolution is considered to be secondary to advancements in preoperative imaging and tumor localization, minimally invasive surgical techniques, and perioperative anesthetic care [2]. Accordingly, recent studies indicate low morbidity rates and a mortality rate close to 0 % [1, 3–5]. Excessive intraoperative catecholamine release during adrenalectomy is thought to occur during endotracheal intubation, creation of pneumoperitoneum, manipulation of the tumor, and dividing the adrenal vein. These maneuvers lead to rapid changes in catecholamine levels and can lead to perioperative morbidity and mortality [5–7].

Intraoperative hemodynamic instability (IHD) has been defined by the occurrence of both hypertensive and hypotensive intraoperative episodes during the same procedure [4]. Historically, the association between IHD and perioperative morbidity dates back to 1956 [8]. Since that time, routine use of alpha blockade and volume expansion has been incorporated into the perioperative optimization of patients prior to surgery, thereby avoiding hemodynamic instability [1, 4, 7, 9, 10]. Although alpha blockade was typically the recommended medical therapy used prior to surgery with phenoxybenzamine, several studies have established the equivalence of calcium channel blockade in the preparation of patients preoperatively for surgical resection [6, 11]. We showed that IHD was independent of type of preoperative medical management and was more dependent on familial disease [12]. As such, clinicians have broader options for preoperative management of pheochromocytoma. Because management of patients with pheochromocytoma has radically evolved since initial reports, the impact of intraoperative hemodynamic instability episodes on postoperative morbidity and mortality has yet to be fully delineated [3, 5, 12]. Thus, the aim of this multicenter study was to determine current perioperative factors that are predictive of postoperative morbidity in patients undergoing laparoscopic adrenalectomy for unilateral pheochromocytoma.

Methods

Patient population

This was a retrospective review of prospectively maintained databases across five medical centers consisting of consecutive patients with unilateral pheochromocytoma at University of Nancy, University of Roma, University of Nantes, Weill Cornell Medical College, and University of Utrecht between 2002 and 2013. In all patients, a transabdominal lateral approach (conventional or robot-assisted) or a retroperitoneal posterior approach was used to perform laparoscopic adrenalectomy [1]. The diagnosis was confirmed in all patients by pathological examination [4]. Patients converted to laparotomy and those who underwent open adrenalectomy were excluded to avoid bias because conversion to laparotomy is associated with higher postoperative morbidity rates [5]. Patients who did not undergo unilateral adrenalectomy (partial adrenalectomy or patients with bilateral tumors) were also excluded. Demographics, serum biochemistries, anesthesia data (particularly intraoperative pharmacologics and hemodynamics), tumor characteristics, and postoperative outcomes were collected in all patients [13]. The institutional review boards at all institutions approved this study.

Preoperative medical preparation (PMP)

Type of medication used for preoperative medical preparation was collected. Nonselective alpha-adrenergic blockade (phenoxybenzamine) and selective α_1-adrenergic blockade (prazosin) were used for alpha blockade (alpha-B) [7]. Calcium channel blockade (CC-B) consisted of a nicardipine regimen [14]. PMP using either alpha-B or CC-B was continued until the date of surgery. Selection of PMP was determined in each medical center by collaboration between surgeons, endocrinologists, and anesthesiologists without preoperative collaboration between the five medical centers.

Operative management

Preinduction blood pressure (BP) was defined as the value assessed the morning of the operation. Adequate preoperative management (blood pressure normalization after preoperative management) was defined by a target preinduction BP of 130/85 mmHg [4, 7, 9]. The calculated mean arterial pressure (MAP) of the target BP value of 130/85 mmHg is 100 mmHg, and this value was also assessed as cutoff value for adequacy [4]. Pneumoperitoneum was achieved by insufflating CO_2 gas to obtain an intraperitoneal pressure of 12 mmHg in all medical centers [15]. During surgery, hypertensive and hypotensive episodes were treated at anesthesiologist's discretion by the use of intravenous drugs. When the main adrenal vein was clamped, antihypertensive drugs and beta-blockers administration were stopped and hemodynamics were reassessed [14].

Intraoperative hemodynamics were assessed using hemodynamic parameters determined from previous studies [4, 13, 16]. The incidence of intraoperative hemodynamic instability (IHD) episodes was also evaluated using five previously published definitions [1, 4, 5, 13, 15, 17]. These five different IHD definitions were the presence of at least one intraoperative SBP $\geq$ 160 mmHg episode, the presence of at least one intraoperative SBP $\geq$ 200 mmHg episode, the presence of at least one mean arterial pressure <60 mmHg episode, the presence of at least one intraoperative SBP $\geq$ 160 mmHg episode associated with at least one intraoperative mean arterial pressure <60 mmHg episode, and the presence of at least one intraoperative SBP $\geq$ 200 mmHg episode associated with at least one intraoperative mean arterial pressure <60 mmHg episode. Incidence of IHD episodes was evaluated in each patient using these five different definitions.

All-cause postoperative complications were collected and classified using Clavien classification [18]. Cardiovascular morbidity was defined as any postoperative morbidity related to the cardiovascular system: postoperative hypotensive or hypertensive episodes requiring pharmacologic management, postoperative bleeding or need for blood transfusions, myocardial or digestive ischemia, stroke, and postoperative hospitalization in intensive care unit (ICU) for cardiac-related causes.

Statistical analysis

Bivariate analyses: Characteristics between groups were compared using the Pearson Chi-square test or Fisher's exact test for categorical variables and the Wilcoxon–Mann–Whitney test for continuous variables. Variables significant at a 0.10 level were subsequently used in multivariate analysis. Multivariate analyses: All-cause morbidity and cardiovascular morbidity outcomes were treated as a dependent variable in logistic regression. Variables significant at a 0.10 level in univariate analysis were used in multivariate analysis. The level of significance for variables retained in the multivariate models was set at 0.05. Data were recorded on Excel files. Statistical analysis was performed using SAS 9.3 statistical software (SAS Institute Inc., NC, USA).

Results

Two-hundred and twenty-five patients underwent unilateral laparoscopic adrenalectomy without conversion for pheochromocytoma. One-hundred and seventy-seven patients (79 %) underwent a lateral transabdominal laparoscopic approach (TransA) and 48 patients (21 %) a posterior laparoscopic approach (RetroA). Mean age, tumor size, and operative time were 50 $\pm$ 16 years, 4.3 $\pm$ 2.0 cm, and 129 $\pm$ 55 min, respectively. Patients and tumor characteristics are reported in Table 1. The type of preoperative medical preparation (PMP) was calcium channel blockade (CC-B) in 110 patients (49 %), alpha blockade (alpha-B) in 108 patients (48 %), and no specific PMP in seven patients (3 %) (Table 2). After PMP, preinduction mean arterial pressure was 100 $\pm$ 15 mmHg in all patients. Adequate blood pressure normalization after PMP, defined either as BP $\leq$ 130/85 mmHg or as mean arterial pressure $\leq$100 mmHg, was observed in 117 patients (52 %) and 121 patients (54 %), respectively (Table 3). We observed that the incidence of patients with familial disease was higher in the RetroA group patients (27 vs. 12 %; $p = 0.022$). Furthermore, the following variables were found to be lower in the RetroA group: tumor size (3.7 $\pm$ 1.8 vs. 4.5 $\pm$ 2.0 cm; $p = 0.009$), preoperative mean metanephrine ratio (4 $\pm$ 5 vs. 9 $\pm$ 12; $p = 0.023$), clinical signs incidence as hypertension (60 vs. 76 %; $p = 0.028$) or headaches (17 vs. 33 %; $p = 0.025$), and ASA score > 2 (12 vs. 54 %; $p = 0.022$). All other criteria in Table 1 were similar between TransA and RetroA group patients (data not shown).

No mortality was observed within the first 30 postoperative days. Postoperative all-cause morbidity and cardiovascular-related morbidity rates were 16 % ($n = 36$) and 4.8 % ($n = 11$), respectively (Table 4). Cardiovascular complications represented 31 % of all 36 postoperative complication causes. Causes for all postoperative complications from Clavien I to Clavien IV are reported in Table 4. Causes for Clavien IV postoperative morbidity were perioperative myocardial stunning requiring ICU admission in three patients and colonic necrosis requiring a reoperation at POD2 in another patient. Overall, mean hospitalization duration was 5.6 $\pm$ 3 days. This duration was longer in patients with postoperative all-cause morbidity (7.3 $\pm$ 5 vs. 5.2 $\pm$ 2 days; $p = 0.001$) and in patients with postoperative cardiovascular-related morbidity (9.1 $\pm$ 7 vs. 5.4 $\pm$ 3 days; $p < 0.001$).

Patients within the postoperative all-cause morbidity group were significantly older, had a larger mean tumor size, and more frequently reported a past medical history of coronary artery disease (Table 1). Similarly, mean number of baseline antihypertensive medications used before PMP and mean number of medications used specifically for PMP were both significantly higher in patients with postoperative all-cause morbidity (Table 3). However, BMI, sex, ASA score, familial disease, preoperative biological workup ratios, clinical signs, comorbidities, and the type of medication used for PMP were not associated with postoperative all-cause morbidity (Tables 1, 3). Also, mean

Table 1 Patients and tumor characteristics in all patients

Criteria	All patients $n = 225$	Without morbidity $n = 189$	With morbidity $n = 36$	p value
Age (years)	50 ± 16	49 ± 16	55 ± 17	0.045
BMI (kg/m2)	25 ± 5	25 ± 4	25 ± 3	0.976
Gender (F/M)	123/102	102/87	21/15	0.629
Tumor size (cm)	4.3 ± 2.0	4.2 ± 1.8	5.0 ± 2.7	0.032
Tumor side (R/L)	120/105	106/83	14/22	0.058
ASA (I–II/III/IV)	117/101/7	98/86/5	19/15/2	0.761
Familial disease	35 (16 %)	29 (15 %)	6 (17 %)	0.840
MEN2	17	13	4	
VHL	10	9	1	
NF1	4	3	1	
SDHx	4	4	0	
Hypertension (%)	164 (73)	136 (72)	28 (78)	0.471
Palpitation (%)	90 (40)	74 (39)	16 (44)	0.552
Sweating (%)	78 (35)	65 (34)	13 (36)	0.842
Headaches (%)	67 (30)	59 (31)	8 (22)	0.279
Normeta ratio[a]	8 ± 10	8 ± 10	8 ± 10	0.983
Meta ratio[a]	8 ± 11	8 ± 11	9 ± 12	0.619
Comorbidities (%)				
Diabetes mellitus	58 (26)	45 (24)	13 (36)	0.122
CAD	25 (11)	16 (8)	9 (25)	0.008
Previous MI	17 (8)	12 (6)	5 (14)	0.159
Previous stroke	9 (4)	7 (4)	2 (5)	0.638

Comparison between patients without ($n = 189$) versus with postoperative all-cause morbidity ($n = 36$)

CAD coronary artery disease, *MI* myocardial infarction

[a] Preoperative biological data were available in 182 patients only

Table 2 Distribution of preoperative medical preparation (PMP) and surgical approach in all patients

Medical center	Patients (n)	TransA/RetroA (n)	CC-B (n)	Alpha-B (n)	No PMP (n)
Utrecht	34	0/34	0	34	0
Cornell	45	45/0	0	41	4
Nantes	39	39/0	39	0	0
Roma	36	22/14	0	33	3
Nancy	71	71/0	71	0	0
All	225	177/48	110	108	7

TransA transperitoneal lateral adrenalectomy, *RetroA* retroperitoneal posterior adrenalectomy, *CC-B* calcium channel blockade, *Alpha-B* alpha blockade, *PMP* preoperative medical preparation

preinduction blood pressure after PMP and incidence of preinduction blood pressure normalization after PMP had no significant impact on postoperative morbidity rate (Table 3).

We observed that intraoperative hemodynamic data were also significantly different between patients with and without postoperative all-cause morbidity (Table 3). Intraoperative hypertensive episodes (duration SBP $\geq$ 160 mmHg; duration SBP $\geq$ 30 % baseline) and hypotensive episodes (lowest systolic BP; lowest mean BP; lowest diastolic BP; duration SBP $\leq$ 30 % baseline; mean BP $<$ 60 mmHg) were more severe in patients with postoperative all-cause morbidity. Intraoperative interval heart rate $\leq$50 beats per minute duration was also higher in postoperative all-cause morbidity group patients (Table 3). Significant preoperative and intraoperative factors between patients with and without postoperative cardiovascular morbidity are summarized in Table 5.

When intraoperative hemodynamic instability (IHD) during adrenalectomy was evaluated using the five previously published IHD definitions described in methods section, IHD incidence ranged from 20 to 69 %. Only four of

Table 3 Preoperative medical preparation (PMP), preinduction and intraoperative hemodynamic data in all patients

Criteria	All patients $n = 225$	Without morbidity $n = 189$	With morbidity $n = 36$	p value
PMP data				
Number of antihypertensive medications before PMP (n)	1.0 ± 1.1	0.9 ± 1.0	1.3 ± 1.6	0.025
Use of antihypertensive medications before PMP (%)	128 (57)	107 (57)	21 (58)	0.848
PMP type (A-B/CC-B/no PMP)	108/110/7	88/94/7	20/16/0	0.364
PMP medications number (n)	1.2 ± 0.5	1.1 ± 0.5	1.3 ± 0.5	0.030
Preinduction data after PMP				
Mean BP (mmHg)	100 ± 15	99 ± 15	102 ± 16	0.277
Mean BP ≤ 100 mmHg (%)	54 %	56 %	44 %	0.205
BP ≤ 130/85 mmHg (%)	52 %	52 %	47 %	0.565
Intraoperative BP data				
Greatest systolic BP (mmHg)	188 ± 45	185 ± 44	200 ± 45	0.084
Greatest mean BP (mmHg)	131 ± 29	130 ± 29	138 ± 29	0.124
Greatest diastolic BP (mmHg)	103 ± 25	102 ± 25	107 ± 29	0.260
SBP ≥ 200 mmHg (min)	3.9 ± 11	3.8 ± 11	4.8 ± 8	0.605
SBP ≥ 160 mmHg (min)	15 ± 19	14 ± 19	21 ± 19	0.042
SBP ≥ 160 mmHg (% Anesth)	7.3 ± 9	6.8 ± 9	10.1 ± 9	0.041
SBP ≥ 30 % baseline (min)	7.3 ± 13	6.3 ± 11	12.6 ± 19	0.009
SBP ≥ 30 % baseline (% Anesth)	3.5 ± 6	3.1 ± 5	5.3 ± 8	0.050
Lowest systolic BP (mmHg)	85 ± 19	87 ± 19	77 ± 16	0.004
Lowest mean BP (mmHg)	61 ± 14	62 ± 14	55 ± 14	0.014
Lowest diastolic BP (mmHg)	49 ± 14	50 ± 13	45 ± 15	0.057
SBP ≤ 30 % baseline (min)	21 ± 30	18 ± 29	31 ± 37	0.021
SBP ≤ 30 % baseline (% Anesth)	10 ± 14	9 ± 13	16 ± 17	0.007
Mean BP < 60 mmHg (min)	6.6 ± 12	5.7 ± 11	11 ± 14	0.011
Mean BP < 60 mmHg (% Anesth)	3.4 ± 6	3.1 ± 6	5.1 ± 6	0.087
Intraoperative heart rate data				
Greatest HR (bts/min)	99 ± 22	99 ± 21	101 ± 27	0.535
Interval HR ≥ 110 (min)	9.1 ± 22	8.8 ± 21	11 ± 29	0.582
Lowest HR (bts/min)	59 ± 13	59 ± 22	58 ± 15	0.933
Interval HR ≤ 50 (min)	4.4 ± 12	3.6 ± 9	8.4 ± 21	0.026

Comparison between patients without ($n = 189$) versus with postoperative all-cause morbidity ($n = 36$)

BP blood pressure, *PMP* preoperative medical preparation, *A-B* alpha blockade, *CC-B* calcium channel blockade, *SBP* systolic blood pressure, *HR* heart rate in beats per minute, *% Anesth* duration expressed as percentage of anesthesia time

these IHD definitions (SBP ≥ 160 mmHg, MAP < 60 mmHg, SBP ≥ 160 mmHg + MAP < 60 mmHg, and SBP ≥ 200 mmHg + MAP < 60 mmHg) were associated with increased postoperative all-cause morbidity (Table 6). With regard to cardiovascular-related morbidity, only three IHD definitions (SBP ≥ 160 mmHg, SBP ≥ 200 mmHg, and SBP ≥ 200 mmHg + MAP < 60 mmHg) were associated with increased morbidity. In univariate analysis, only two IHD definitions (SBP ≥ 160 mmHg and SBP ≥ 200 mmHg + MAP < 60 mmHg) were associated with increased all-cause and cardiovascular morbidity (Table 6).

On multivariate analysis, past medical history of coronary artery disease (OR [CI95 %] = 3.39; [1.317–8.727]) and incidence of SBP ≥ 160 mmHg + MAP < 60 mmHg intraoperative episode (OR [CI95 %] = 3.092; [1.451–6.587]) remained independent predictors for postoperative all-cause morbidity. With regard to cardiovascular-related morbidity, we observed that past medical history of coronary artery disease (OR [CI95 %] = 14.41; [3.119–66.57]), female sex (OR [CI95 %] = 12.05; [1.807–80.31]), and incidence of SBP ≥ 200 mmHg + MAP < 60 mmHg intraoperative episode (OR [CI95 %] = 4.13; [1.009–16.90]) remained independent predictors for postoperative cardiovascular-

Table 4 Causes for postoperative morbidity using Clavien classification

	All patients $n = 225$
Clavien I	11 (4.8 %)
Abdominal pain	3
Postoperative confusion	2
Wound hematoma	2
Atelectasia	2
Allergic skin reaction	2
Clavien II	21 (9.3 %)
Pneumonia	3
Hyperthermia	3
Postoperative hypertension	3
Wound infection	2
Transfusion	2
Allergy	2
UTI	2
Postoperative hypotension	2
Pancreatitis	1
Delirium tremens	1
Clavien III	0 (0 %)
Clavien IV	4 (1.7 %)
Myocardial stunning in ICU	3
Colonic necrosis	1
All morbidity causes (Clavien I–IV)	36 (16 %)
Cardiovascular morbidity causes	11 (4.8 %)
Postoperative hypertension	3
Myocardial stunning in ICU	3
Transfusion	2
Postoperative hypotension	2
Colonic necrosis	1

UTI urinary tract infection, *ICU* intensive care unit

related morbidity (Table 7). In clinical practice, this analysis showed that a patient with a past medical history of coronary artery disease and intraoperative SBP $\geq$ 160 mmHg + MAP < 60 mmHg episode had a 6.4 times higher risk of developing postoperative all-cause morbidity. Similarly, a female patient with a past medical history of coronary artery disease and an intraoperative SBP $\geq$ 200 mmHg + MAP < 60 mmHg episode had a 30.5 times higher risk of developing postoperative cardiovascular morbidity.

Discussion

This multicenter study identifies preoperative and intraoperative predictive factors for postoperative morbidity after unilateral laparoscopic adrenalectomy. Major factors that impacted independently all-cause morbidity and cardiovascular morbidity included past medical history of coronary artery disease and intraoperative hemodynamic instability. Additionally, female sex was also an independent predictor for postoperative cardiovascular morbidity.

Surgery for pheochromocytoma carries a risk of intraoperative hemodynamic instability [4, 5, 17]. Incidence of intraoperative hemodynamic instability episodes during laparoscopic adrenalectomy for pheochromocytoma ranged from 17 to 83 %, which correlates with the findings in our study [1, 4, 13, 19–21]. In early studies, life-threatening intraoperative catecholamine release had been quickly identified as the causes of blood pressure variability and various cardiac arrhythmias leading to perioperative morbidity and mortality [3, 4, 8, 10]. Since then, intraoperative hemodynamic instability episodes were considered to be related to postoperative morbidity and mortality rates. This correlation led to the worldwide consensus that all patients with hormonally functional pheochromocytoma should undergo preoperative medical preparation with antihypertensive therapy for preoperative blood pressure normalization to improve intraoperative hemodynamic instability and perioperative morbidity and mortality [4, 7, 10, 13, 16]. However, this study showed that among five published definitions of intraoperative hemodynamic instability, only two have a significant impact on postoperative morbidity in multivariate analysis (SBP $\geq$ 160 mmHg + MAP < 60 mmHg and SBP $\geq$ 200 mmHg + MAP < 60 mmHg). Interestingly, our prior study showed that intraoperative hemodynamic instability did not impact postoperative morbidity rates (24 vs. 13 %; $p = 0.12$) [12]. This difference is most likely due to the larger sample size. We believe that the two IHD definitions identified as predictive for postoperative morbidity in this study could become intraoperative targets for surgeons and anesthesiologists. Furthermore, they could be used as consensual IHD definitions in further studies evaluating laparoscopic adrenalectomy for unilateral pheochromocytoma.

This study showed that past medical history of coronary artery disease and female sex was also a significant risk factor for postoperative morbidity. It was recently shown that pheochromocytoma patients have a clearly higher rate of cardiovascular events than patients with essential hypertension [22], which suggests that these events cannot be attributed solely to differences in blood pressure or other cardiovascular risk factors. Instead, in pheochromocytoma patients, prolonged exposure to the elevated levels of circulating catecholamines on the myocardium and coronary arteries may have additional toxicity to the vasculature [22]. Although nonreversible, we believe these two criteria should be taken into account in patients scheduled for laparoscopic adrenalectomy for pheochromocytoma.

Overall, similar to prior reports the morbidity of adrenalectomy for pheochromocytoma ranges from 0 to

Table 5 Preoperative and intraoperative criteria with significant difference ($p < 0.05$) between patients without ($n = 214$) versus with postoperative cardiovascular morbidity ($n = 11$)

Criteria	Without morbidity $n = 214$	With morbidity $n = 11$	p value
Comorbidities (%)			
Diabetes mellitus	52 (24)	6 (55)	0.035
CAD	20 (9)	5 (45)	0.003
PMP data			
Number of antihypertensive medications before PMP (n)	0.9 + 0.9	2.3 + 2.1	0.018
Intraoperative BP data			
Greatest systolic BP (mmHg)	187 + 45	207 + 22	0.021
Greatest mean BP (mmHg)	130 + 29	147 + 19	0.009
Greatest diastolic BP (mmHg)	102 + 25	118 + 25	0.028
SBP > 160 mmHg (min)	15 + 19	29 + 20	0.004
SBP > 160 mmHg (% Anesth)	7.0 + 9	14 + 9	0.003

CAD coronary artery disease, *PMP* preoperative medical preparation, *BP* blood pressure, *% Anesth* duration expressed as percentage of anesthesia time

Table 6 Intraoperative hemodynamic instability (IHD) incidence using five previously published IHD definitions in patients with and without postoperative morbidity (univariate analysis)

IHD definitions (at least one episode during adrenalectomy)[a]	IHD incidence (%)			
	In all patients $n = 225$ (%)	In patients with morbidity $n = 36$ (%)	In patients without morbidity $n = 189$ (%)	p** value
All-cause morbidity				
SBP > 160 mmHg	69	83	66	0.049
SBP > 200 mmHg	33	46	31	0.086
MAP < 60 mmHg	49	67	46	0.027
SBP > 160 mmHg + MAP < 60 mmHg	36	56	32	0.003
SBP > 200 mmHg + MAP < 60 mmHg	20	36	17	0.008
	$n = 225$ (%)	$n = 11$ (%)	$n = 214$ (%)	
Cardiovascular morbidity				
SBP > 160 mmHg	69	100	68	0.019
SBP > 200 mmHg	33	64	32	0.044
MAP < 60 mmHg	49	70	48	0.207
SBP > 160 mmHg + MAP < 60 mmHg	36	64	35	0.102
SBP > 200 mmHg + MAP < 60 mmHg	20	45	19	0.047

SBP systolic blood pressure, *MAP* mean arterial pressure

** p value for IHD incidence between patients with and without postoperative morbidity

[a] Five previously published different IHD definitions were used to define intraoperative hemodynamic instability (at least one episode during adrenalectomy)

20 % [1, 5, 13, 19, 20, 23–26]. Given the perioperative optimization of patients with these tumors, the mortality of this surgical approach reaches 0 %. Postoperative complications after adrenalectomy for pheochromocytoma are not uniform throughout the literature and are divided into several categories [2, 26]. We used the Clavien classification to better describe the nature of postoperative complications in our cohort [18]. Since patients with pheochromocytoma have a 14-fold higher rate of cardiovascular events than patients with essential hypertension,

Table 7 All-cause morbidity and cardiovascular morbidity outcomes were treated as a dependent variable in logistic regression (multivariate analysis)

	Bivariate regression			Multivariate regression	
	OR	95 % CI	*p*	OR	95 % CI
All-cause morbidity					
CAD	3.604	1.448–8.970	0.008	3.390	1.317–8.727
IHD 160	2.987	1.439–6.198	0.003	3.092	1.451–6.587
interval HR $\leq$ 50 (min)	1.025	1.000–1.052	0.051		
IHD 200	2.755	1.264–6.006	0.013		
Age (years)			0.005		
Tumor size (cm)	1.018	1.001–1.035	0.037		
Tumor side (R/L)			0.057		
Medical center			0.032		
Cardiovascular morbidity					
CAD	8.083	2.263–28.87	0.002	14.41	3.119–66.57
Female gender	3.947	0.833–18.70	0.052	12.05	1.807–80.31
IHD 200	3.604	1.048–12.40	0.050	4.130	1.009–16.90
Diabetes mellitus	3.738	1.096–12.76	0.037		
AHM before PMP (*n*)	2.435	1.087–5.453	0.022		

CAD coronary artery disease, *IHD 160* incidence of SBP $\geq$ 160 mmHg + MAP < 60 mmHg intraoperative episode, *IHD 200* incidence of SBP $\geq$ 200 mmHg + MAP < 60 mmHg intraoperative episode, *PMP* preoperative medical preparation, *AHM* antihypertensive medications

we also separated cardiovascular-related morbidity from all-cause morbidity [22]. Accordingly, Shen et al. [26] reported in 102 patients that cardiovascular complications represented 22 % of all-cause postoperative morbidity, which is slightly lower than our findings (36 %). This may be due to the larger sample size or the variability due to multiple clinicians performing this surgery at several institutions.

Similar to prior reports, we observed that retroperitoneal approach was performed in patients with smaller tumors [20, 25]. We also found that the type of medications used for preoperative management (alpha blockade vs. calcium channel blockade) and preinduction blood pressure normalization after preoperative medical preparation has no significant impact on postoperative morbidity rate [3, 12, 27]. These data raise into question recent guidelines recommending preoperative medical treatment to normalize preinduction blood pressure [10]. We believe further studies are needed to evaluate this last issue [3, 27].

There are several limitations to this study. First, this was a retrospective study between five different medical centers, which was necessary to permit adequate numbers of patients for multivariate analysis. A second limitation is the likely variability of anesthetic and surgical management between medical centers, which could potentially bias this study results toward one institution's management. More specifically, no uniformity in intraoperative anesthesia management across medical centers could also bias this study conclusions. Third, laparoscopic adrenalectomy was performed using retroperitoneal and transabdominal conventional laparoscopic and robot-assisted approaches. Although a wide range of laparoscopic approaches can strengthen the study's conclusions, we acknowledge that this study was underpowered to assess differences in IHD and postoperative outcomes between different approaches. To address these limitations, a randomized trial is required. Furthermore, to limit bias we compared our overall patient characteristics (past medical history, comorbidities, symptoms, tumor size and secretion, preoperative medical preparation type, preinduction blood pressure normalization) and postoperative morbidity rates in this study were similar compared to other recent reports [4, 5, 13, 22].

In conclusion, this study showed that risk factors for postoperative morbidity after laparoscopic adrenalectomy are history of coronary artery disease, female gender, and intraoperative hemodynamic instability episode defined as SBP $\geq$ 200 and MAP < 60 mmHg during the same procedure. Preinduction blood pressure normalization after preoperative medical preparation had no impact on postoperative morbidity. Those criteria should be taken into account in further studies and can help physicians to guide intra-operative blood pressure management.

Disclosures Brunaud, Nguyen-Thi, Mirallie, Raffaelli, Vriens, Theveniaud, Boutami, Finnerty, Vorselaars, Borel Rinkes, Bellantone, Lombardi, Fahey, Zarnegar, and Bresler have no conflict of interest or financial ties to disclose.

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