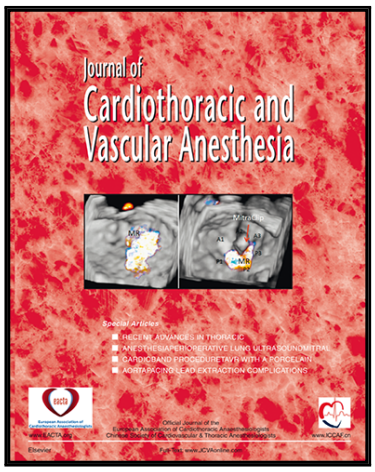

Prognostic model for vasopressors requirement after retroperitoneal adrenalectomy for pheochromocytoma. A retrospective study.

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Prognostic model for vasopressors requirement after retroperitoneal adrenalectomy for pheochromocytoma. A retrospective study.

Sergey Efremov[1], Mikhail Alexeev[1], Oleg Kuleshov[1], Alexander Safronov[1], Vyacheslav Ryndin[3], Dina Rebrova[2], Elisei Fedorov[2]

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Abstract

Objectives. To evaluate the risk factors for postoperative vasopressor requirement among patients with pheochromocytoma undergoing retroperitoneal adrenalectomy. The primary outcome was postoperative hypotension requiring vasopressor support.

Design. A single-center retrospective observational study.

Setting. University hospital.

Participants. Adults who underwent unilateral adrenalectomy for pheochromocytoma between October 2015 and February 2020.

Interventions. None.

Measurements and Main Results. Overall, 201 patients were included. Postoperative vasopressor requirement was observed in 39 (19.4%) patients and is associated with baseline coronary artery disease (CAD) [odds ratio (OR) 6.21, 95% confidence interval (CI) 2.48–15.52; p = 0.0001], maximal systolic blood pressure (maxSBP) >195 mmHg (OR 3.71, 95% CI 1.53–8.95; p = 0.0035), and >5.1-fold increase in the upper limit of normal values for baseline adrenergic activity (OR 4.9, 95% CI 1.93–12.55; p = 0.0008). The area under receiver operating characteristic curve of the predictive model was 0.804 (95% CI 0.742–0.856).

Conclusion. MaxSBP >195 mmHg, baseline adrenergic activity >5.1-fold increase in the upper limit of normal values, and baseline CAD could predict post-resection requirement for vasoactive support. Prospective multicenter international studies are required to develop and validate universally accepted predictive models for postoperative complications in patients after adrenalectomy for pheochromocytoma.

Introduction

Hypotension is the most common postoperative complication in patients undergoing pheochromocytoma resection.[1] Prolonged preoperative elevation of blood catecholamine concentrations reportedly leads to circulating blood volume depletion and downregulation of adrenoreceptors and is responsible for postoperative hypotension, which necessitates vasopressor support and patient management in the intensive care unit (ICU).[2]

Anesthetic management of patients with pheochromocytoma is often challenging because of the highly variable hemodynamic alterations at different stages of surgery. Despite the number of previously reported baseline risk factors for perioperative hypotension (tumor size, urinary catecholamines, open surgery, maximum prehospital systolic blood pressure [maxSBP], diabetes mellitus, and preoperative alpha-adrenoreceptor blockers), there is still no universally recognized risk stratification tool for patients with pheochromocytoma.[3–7] The rarity of pheochromocytoma explains the retrospective design of the available studies with highly variable definitions of hypotension and postoperative complications.

The aim of the present retrospective study was to develop a prognostic equation for the probability of postoperative vasopressor requirement among patients with pheochromocytoma undergoing retroperitoneal adrenalectomy.

Methods

Study design

This was a retrospective, observational study. The local ethics committee of Saint-Petersburg State University Hospital waived the requirement for ethical approval due to the retrospective nature of the study.

Study population

The inclusion criteria were as follows: (1) age ≥18 years and (2) unilateral posterior retroperitoneoscopic adrenalectomy for pheochromocytoma performed between October 2015 and February 2020.

The exclusion criteria were (1) lack of data on baseline urinary metanephrines or perioperative vasoactive support, (2) intraoperative conversion to open adrenalectomy, (3) postoperative histological exclusion of pheochromocytoma, and (4) bilateral adrenalectomy.

Data were extracted from electronic medical records and collected in an electronic database (Excel, Microsoft®).

Study outcomes

The primary outcome was postoperative hypotension (mean BP <65 mmHg) requiring vasopressor support. The secondary outcomes were (1) postoperative

complications, (2) peak perioperative vasoactive inotropic score (VIS), and (3) length of hospital stay.

VIS was determined using the following formula: VIS = dopamine dose (μg/kg/min) + dobutamine dose (μg/kg/min) + 100 × epinephrine dose (μg/kg/min) + 10 × milrinone dose (μg/kg/min) + 10,000 × vasopressin dose (U/kg/min) + 100 × norepinephrine dose (μg/kg/min).[8]

Postoperative complications were defined as any of the following conditions during hospitalization: bleeding, stroke, myocardial infarction, or hypoglycemia.

Exposure variables

The exposure variables were: (1) urinary or blood catecholamine metabolite (metanephrine and/or normetanephrine) levels expressed in multiplicity of exceeding the upper limit of normal values, (2) maxSBP, (3) daily dose of alpha-blockers, (4) chronic administration of beta-blockers, (5) history of CAD, (6) tumor size assessed on tomography, (7) age, and (8) sex.

Clinical evaluation

Patients were hospitalized at least 1 day before surgery. Pheochromocytoma was diagnosed during the prehospital period based on clinical signs, contrast-enhanced computed tomography findings, and laboratory evaluation of adrenergic activity (catecholamine metabolites). In some patients, pheochromocytoma was asymptomatic without any laboratory or imaging signs. In these cases, only postoperative histological verification was used to confirm the diagnosis. Before surgery, patients with preoperatively diagnosed pheochromocytoma were infused with 1500–2000 ml crystalloids in the ward over 24 hours. All patients continued their regular medications until the day of surgery.

The patients underwent surgery under general anesthesia. Anesthesia was induced with 2 mcg\kg fentanyl, 2 mg/kg propofol, and 0.6 mg/kg rocuronium and was maintained with sevoflurane or desflurane in 1–2 L/min of fresh gas with 50% oxygen fraction. Minimal intraoperative monitoring included electrocardiography, body temperature, end-tidal CO_2, arterial line BP, central venous pressure, arterial blood gases, bispectral index, and pulse oximetry. Additionally, at the discretion of the anesthesiologist, intraoperative advanced hemodynamic monitoring with transpulmonary thermodilution was performed in 50 patients (the advanced hemodynamic data for these patients have been previously published). [9]

All surgeries were performed with the patients in prone position lying on a rectangular support using the posterior retroperitoneoscopic approach described by Walz et al. by a single surgeon. [10]

Perioperative hypotension was defined as mean BP <65 mmHg and was treated with intravenous fluids and/or infusion of catecholamines (norepinephrine, epinephrine, dopamine, or phenylephrine). The volume of intraoperative infusion was initially set at 3 ml/kg/h of crystalloids and further adjusted according to the fluid status and fluid responsiveness, as assessed by available static and dynamic methods. The first-line vasopressor of choice was norepinephrine; a second or third catecholamine was added, if required. Hypertension (if associated with tachycardia of >100 beats per minute) was treated with esmolol and/or nitroglycerin. The drug/s of choice was/were administered at the discretion of the anesthesiologist. All patients with postoperative vasoactive support were transferred to ICU.

Statistical analysis

As this was a retrospective observational study, formal power analysis was not performed. Categorical data are presented as numbers and percentages, and continuous variables as medians and 25th and 75th percentiles. Normality was tested using the Shapiro–Wilk normality test. Correlation analysis was performed to assess collinearity. Univariate and stepwise multivariate logistic regression analyses were performed to develop a predictive equation for the postoperative vasopressor requirement. Categorization of variables was performed using receiver operating characteristic (ROC) analysis. Results are expressed as odds ratio (OR) with 95% confidence interval (CI) and area under ROC curve (AUC). P-values of <0.05 were considered a cut-off point for statistical significance, and all statistical tests were two-sided. Statistical analyses were performed using the MedCalc statistical software version 20.123 (MedCalc Software bvba, Ostend, Belgium).

Results

A total of 207 patients with pheochromocytoma who underwent retroperitoneoscopic adrenalectomy between October 2015 and February 2020 were assessed for eligibility. Three patients were excluded owing to emergency conversion to open surgery and another three were excluded due to loss of vasoactive support data. Ultimately, 201 patients were included in this analysis. Baseline and perioperative clinical data and outcomes are presented in Table 1.

Predictors of postoperative vasopressor support

In total, 39 (19.4%) patients required vasopressor support after the end of anesthesia.

A weak correlation was found between tumor size and blood catecholamine concentration ($r = 0.41$, $p < 0.0001$).

The results of univariate and multivariate logistic regression analyses for predictors of postoperative vasopressor requirement using the original data are presented in Table 2 (model 1). The logistic regression equation of model 1 is:

Logit(p) = −7.65 + 1.72 × CAD + 0.026 × maxSBP + 0.061 × adrenergic activity.

The AUC of model 1 was 0.841 (95% CI 0.783–0.889), confirming its good discriminative value. At the individual level, the logit(p) could be further transformed into the probability of a requirement for postoperative vasopressor support using the logit table of formulas available elsewhere.

Additionally, to improve the practical convenience of the predictive model, the continuous variables (maxSBP and adrenergic activity) were dichotomized using ROC analysis.

The threshold value for maxSBP was 195 mmHg (sensitivity 76.9%; specificity 64.8%; AUC 0.77, 95% CI 0.71–0.83; $p < 0.001$) (Figure 1). The threshold value of adrenergic activity was a 5.1-fold increase in catecholamine metabolite concentrations (sensitivity 79.5%, specificity 59.9%, AUC 0.72, 95% CI 0.65–0.78; $p < 0.001$) (Figure 2).

The final logistic regression analysis using the modified (dichotomized) variables is presented in Table 2 (model 2). The AUC of model 2 was 0.804 (95% CI 0.742–0.856), confirming its good discriminative value.

Discussion

In accordance with the results of the presented study, CAD, peak prehospital SBP, and baseline adrenergic activity are predictors of the post-resection requirement for vasoactive support.

Intraoperative vasopressor requirement is common during pheochromocytoma resection in almost every patient. In our study, 19.4% of the patients required postoperative vasopressors. It is believed that post-resection hypotension develops due to an abrupt decrease in circulating catecholamines owing to chronically downregulated adrenergic receptors and low circulating blood volume.[1,4,7,11,12] However, in a majority of patients, vasopressor support is discontinued at the end of surgery, making it possible for the patient to be transferred to the postanesthetic care unit or surgical ward depending on local hospital policy. The incidence of postoperative vasopressor requirement requiring patient transfer to ICU is variable among studies, ranging from 11% [4] to 46%.[12] Large variability in perioperative hemodynamic alterations has also been reported in a multicenter retrospective study of 159 patients who underwent surgery in 10 Spanish hospitals over a decade (2011–2021).[7]

Despite the long history of pheochromocytoma treatment, there is no international consensus on the risk factors for postoperative complications. Pheochromocytomas and other catecholamine-producing tumors are rare diseases with a low frequency of mortality and morbidity.[5] Complications and critical incidents described in early studies, such as perioperative hypertension or peak values of vasoactive support, did not affect mortality, hospital stay, or cost of treatment.[13] The aim of the present study was to evaluate the predictive value of preoperative factors for post-resection vasopressor requirement, and as a result, the absolute need for postoperative ICU stay.

It is not remarkable to find CAD-predicted postoperative vasopressor support as it is a well-known prognostic factor for adverse cardiovascular outcomes in non-cardiac surgery.[19] Unfortunately, retrospective data do not allow a deep analysis

of the mechanisms underlying this finding, as cardiac troponin measurement has not been performed.

Comparison with previous studies

In a retrospective study of 100 patients operated on over a 20-year period (1992–2013), Livingstone et al. found intraoperative magnesium and preoperative SBP as the predictors of intraoperative hemodynamic instability.[5] In their study, hemodynamic instability was defined as >10 episodes of hypotension or hypertension requiring intervention with vasoactive drugs. A similar approach in the definition of the endpoint as a combination of hypotension and hypertension was used in the study by Jiang et al., who retrospectively evaluated predictors of hemodynamic instability among 134 Chinese patients.[3] The authors found that tumor diameter >50 mm (OR 2.5 [95% CI 1.1–5.5]), diabetes/prediabetes (OR 2.2 [95% CI 1–4.9]), and baseline SBP fluctuation >50 mmHg (OR 3.1 [95% CI 1–9.5]) were predictors of hemodynamic instability. In contrast to the aforementioned studies, we focused on the predictors of postoperative hypotension requiring vasopressors as an endpoint. As we have shown previously, the predictors of perioperative hypotension and hypertension may not be uniform.[9] In particular, baseline blood pressure, as a predictor of vasopressor support, may not be associated with the requirement for vasodilators. This might be explained by the differences in the underlying mechanisms of perioperative hypotension and hypertension.[11,12] Thus, we believe that hypotension and hypertension should not be combined as one endpoint.

Although both perioperative hypotension and hypertension are associated with adverse clinical outcomes, we focused on postoperative vasopressor requirement as an endpoint with clear clinical relevance.[14] Using VIS as a measure of hemodynamic

instability may be preferable over hypotension (commonly defined as BP values below predefined threshold). In a retrospective study by Namekawa et al., hypotension was defined as SBP <90 mmHg and was predicted by tumor size >60 mm (OR 24.9 [95% CI 2.8–591.5]), preoperative urinary epinephrine >200 µg/d (OR 10.7 [95% CI 2.4–62.3]), and preoperative urinary norepinephrine >600 µg/d (OR 4.6 [95% CI 1.3–18]).[12] We believe that VIS, being a measure of efforts required to avoid or treat hypotension, better reflects hemodynamic instability rather than hypotension; therefore, VIS should always be assessed when hypotension is a variable of interest.[15]

Tumor size predicted postoperative vasopressor requirement in a number of studies, but this relationship was not supported by our results despite the expectation of high collinearity between tumor size and catecholamine metabolite levels.[4,12,16,17] This could be explained by differences in the methods used to assess tumor size. Considering the common non-spherical tumor shape, we estimated tumor size as a volume expressed in cm^3 in contrast to previous studies that measured tumor diameter. Another possible explanation, at least partially, may be based on the observation of a negative relationship between tumor size and its function, as large tumors tend to be structurally more heterogeneous due to increasing amounts of hemorrhage, necrosis, and fibrosis.[18] However, we also found a weak correlation between tumor size and catecholamine metabolite levels.

The necessity of preoperative alpha-blockade has been discussed previously.[1,5,20,21] Groeben et al. have shown that preoperative alpha-blockers predicting perioperative hypotension and vasopressor requirements do not affect episodes of hypertension.[21] Our study also found an increased dose-dependent risk of postoperative vasopressor requirement among patients who received alpha-blockers in the univariate analysis, but this variable was not included in the multivariate model.

Study limitations

Our study has some limitations. The first limitation is its retrospective design, which is typical for rare disease studies. Until now, the majority of published pheochromocytoma studies have been retrospective. Second, the heterogeneity of available tests for metanephrines forced us to express this variable as multiplicity exceeding the upper limit of normal values. Third, the lack of routine postoperative measurement of troponin indicated that this factor could not be used to assess myocardial damage, which can play a role in vasopressor requirement, especially in patients with CAD. Lastly, this study was based in a derivation dataset for predictive model development and should be validated prospectively. However, considering the rarity of pheochromocytoma, such a validation study would be more appropriate for a multicentric design.

In conclusion, the likelihood of post-resection vasoactive support increases among patients with baseline CAD, preoperative maxSBP >195 mmHg, and baseline adrenergic activity >5.1-fold increase in the upper limit of normal values. Prospective multicenter international studies are required to develop and validate a universally accepted predictive model for postoperative complications in patients after adrenalectomy for pheochromocytoma.

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Figure legends

Fig. 1 The ROC curve of maxSBP.

The point of separation for a maxSBP >195 with a sensitivity of 76.9% and specificity of 64.8% significantly separates patients who required postoperative vasopressor support (OR, 6.14; CI, 2.73–13.82; $p < 0.0001$).

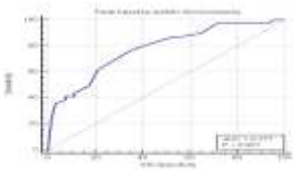
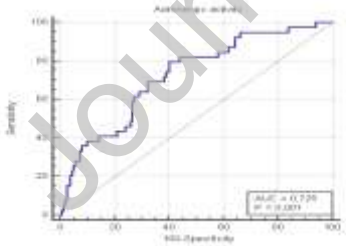


Fig. 2 The ROC curve of adrenergic activity.

The point of separation for adrenergic activity >5.1 fold exceeding the upper limit of normal values of urinary or blood catecholamine metabolites with a sensitivity of 79.5% and specificity of 59.9% significantly separates patients who required postoperative vasopressor support from those who did not (OR, 5.63; CI, 2.44–13.03; $p = 0.0001$).



Statements & Declarations

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Competing Interests

The authors have no relevant financial or non-financial interests to disclose.

Author Contributions

Efremov S and Alexeev M contributed to the study conception and design. Material preparation, data collection and analysis were performed by Alexeev M, Safronov A, Ryndin V, Rebrova D, Fedorov E and Kuleshov O. The first draft of the manuscript was written by Efremov S and Alexeev M and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Table 1. Demographics, perioperative and outcome data

Variable	Without postoperative vasopressors	With postoperative vasopressors	P
Demographics			
Number of patients	162 (80.6)	39 (19.4)	
Females	111 (68.5)	26 (66.7)	0.82
Age, years	46 (37; 57)	51 (40; 63)	0.13
Body Mass Index, kg/m	25 (22; 28)	25 (23; 28)	0.64
Alpha-Blockers administration	117 (72.2)	35 (89.7)	0.02
Beta-blockers administration	16 (9.9)	6 (15.4)	0.29
ASA 2	58 (35.8)	2 (5.1)	0.0002
ASA 3	104 (64.2)	37 (94.9)	
Adrenergic Activity*			
Coronary Artery Disease	18 (11.1)	18 (46.2)	<0.0001
Tumor Size, cm3	40 (30; 50)	40 (34; 60)	0.37
Intraoperative characteristics			
Duration of surgery, min	80 (65; 115)	105 (70;170)	0.001
Intraoperative fluid infusion, ml	2000 (1550; 2500)	2700 (2100; 3262)	<0.0001
Urine output, ml	300 (150; 500)	500 (300; 800)	0.0004
Norepinephrine requirement	113 (69.8)	36 (92.3)	0.004
Epinephrine	34 (21)	30 (76.9)	<0.0001

Dopamine	26 (16)	18 (46.2)	<0.0001
Phenylephrine	2 (1.2)	3 (7.7)	0.02
Esmolol	61 (37.7)	25 (64.1)	0.003
Nitroglycerine	94 (58)	33 (84.6)	0.002
Peak VIS**	20 (6; 40)	56 (30; 82)	<0.0001
Peak VIS 0-5	40 (24.7)	0	<0.0001
Peak VIS 6-10	23 (14.2)	1 (2.6)	
Peak VIS 11-20	28 (17.3)	4 (10.3)	
Peak VIS 21-50	49 (30.2)	13 (33.3)	
Peak VIS >50	22 (13.6)	21 (53.8)	
Cumulative dose of norepinephrine, mg	0.4 (0.08; 1.16)	2 (1.15; 3.92)	<0.0001
Peak dose of nitroglycerine, mcg/kg/min	1.78 (0; 6.2)	10.9 (3.5; 13.9)	<0.0001
Cumulative dose of nitroglycerine, mg	2 (0; 8.8)	14 (3.8; 40)	<0.0001
Peak dose of esmolol, mcg/kg/min	0 (0; 42)	21.9 (0; 100.2)	0.002
Cumulative dose of esmolol, mg	0 (0; 58)	50 (0; 209)	0.0006
Outcomes			
Hyperglycemia (>10 mmol/l)	64 (39.5)	30 (76.9)	<0.0001
Hypoglycemia (<4,1 mmol/l)	2 (1.2)	0	0.49
Bleeding needing transfusion	0	4 (10.2)	<0.0001
Myocardial infarction	0	1 (2.5)	0.04
Arterial thrombosis	1 (0.6)	2 (5.1)	0,03
Venous thromboembolism			
Stroke			
Death			
Postoperative admission to ICU	106 (65.4)	39 (100)	<0.0001
ICU stay, nights#	1 (0; 1)	1 (1; 1)	<0.0001
Hospital stay, nights	4 (4; 5)	5 (4; 8)	0.0001

* - multiplicity of exceeding the upper limit of normal values of catecholamines as they are or their metabolites in blood or urine depending of method of measuring

** - Vasoactive Inotropic Score (VIS) is equal to dopamine dose (µg/kg/min) + dobutamine dose (µg/kg/min) + 100 x epinephrine dose (µg/kg/min) + 10 x milrinone dose (µg/kg/min) + 10,000 x vasopressin dose (U/kg/min) + 100 × norepinephrine dose (µg/kg/min).[8]

- Among patients admitted to ICU postoperatively.

Table 2. Logistic regression analysis for predictors of postoperative vasopressor requirement.

Variable	Univariate analysis		Multivariate analysis – model 1		Multivariate analysis – model 2	
	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
Age, years	1.02	0.1				

	(0.99-1.05)					
BMI						
Alphablockers dose. mg	**1.15 (1.06-1.25)**	**0.0006**	1.02 (0.9-1.13)	0.65	1.06 (0.96-1.17)	0.25
Treatment with beta blockers	1.71 (0.62-4.71)	0.29				
Peak baseline DBP, mm Hg[$]	**1.03 (1.01-1.05)**	**0.002**				
Tumor size. cm3	1.01(0.99-1.03)	0.1				
Intraoperative fluid volume, ml/kg						
CAD	**6.86 (3.09-15.23)**	**<0.0001**	**5.6 (2.2-14.3)**	**0.0003**	**6.21 (2.48-15.52)**	**0.0001**
Peak baseline SBP, mm Hg	**1.03 (1.02-1.04)**	**<0.0001**	**1.02 (1.01-1.04)**	**<0.0001**	_____	
Adrenergic activity*	**1.06 (1.03-1.09)**	**0.0003**	**1.06 (1.02-1.1)**	**0.001**	_____	
Peak baseline SBP >195 mm Hg	**6.14 (2.73-13.82)**	**<0.0001**	_____		**3.71 (1.53-8.95)**	**0.0035**
Adrenergic activity* > 5.1-fold	**5.63 (2.44-13.03)**	**0.0001**	_____		**4.9 (1.93-12.55)**	**0.0008**

Values are presented as odds ratio with 95% confidence interval (OR (95% CI))

VIS - Vasoactive Inotropic Score (VIS) is equal to dopamine dose (μg/kg/min) + dobutamine dose (μg/kg/min) + 100 x epinephrine dose (μg/kg/min) + 10 x milrinone

dose (µg/kg/min) + 10.000 x vasopressin dose (U/kg/min) + 100 × norepinephrine dose (µg/kg/min)

BMI – body mass index

MAP - mean arterial pressure. mm Hg

CAD - coronary artery disease

SBP - systolic blood pressure. mm Hg

DBP - diastolic blood pressure. mmHg

[$] Was not included into the multivariate analysis due to high collinearity with peak baseline SBP.

*Multiplicity of exceeding the upper limit of normal values of urinary or blood catecholamine metabolites (metanephrine and/or normetanephrine)

Graphical Abstract