Am J Cancer Res 2023;13(4):1602-1610
www.ajcr.us /ISSN:2156-6976/ajcr0149465

Brief Communication

Nomogram for predicting hemodynamic instability and the association between preoperative 3D printing and hemodynamic instability during laparoscopic adrenalectomy for pheochromocytoma

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Received February 2, 2023; Accepted April 6, 2023; Epub April 15, 2023; Published April 30, 2023

Abstract: Laparoscopic adrenalectomy (LA) for resection of pheochromocytomas (PCCs) is associated with high risk of complications and morbidity due to intraoperative hemodynamic instability (HDI). This study aims to identify factors related to HDI during laparoscopic resection of pheochromocytoma and develop a scoring model for prediction of HDI. Data of a total of 119 patients with pathological confirmed PCCs were collected at a single center in China between 2010 and 2021. All patients underwent unilateral LA for PCCs. Clinical and biochemical variables were collected. Next-generation sequencing was performed in all PCCs patients for detection of mutations. Univariate and multivariable logistic regression analyses were used to select risk factors for constructing the nomogram. The area under the receiver operating characteristic (ROC) curve (AUC) was used to evaluate the discrimination of the nomogram. The calibration curve was performed. Finally, four variables including 24 h urinary output of urine vanillylmandelic acid (VMA) ≥ 58 μmol/day, tumor size ≥ 4 cm, right-side tumor location, Cluster 2 mutations were independent risk factors for HDI during LA and were included in the nomogram. The nomogram demonstrated a good discrimination performance with an AUC of 0.784 [95% confidence interval (CI), 0.701-0.867]. The calibration curve showed a bias-corrected AUC of 0.758. Multivariable analysis revealed that preoperative 3D printing is an independent protective factor for HDI. Our study proposed a novel nomogram for prediction of HDI during LA for resection of PCCs. Preoperative 3D printing was associated with HDI in PCCs.

Keywords: Pheochromocytoma, laparoscopic adrenalectomy, hemodynamic instability, cluster 2 mutation, 3D printing, nomogram

Introduction

Pheochromocytomas (PCCs) are rare catecholamine-producing tumors originating from the adrenal chromaffin [1-3]. PCCs can secrete excessive catecholamines, which may cause endocrine hypertension [3]. Surgery resection remains the curative treatment for PCCs and minimally invasive procedures have now become the first choice of surgery [4-6]. Compared to open adrenalectomy (OA), laparoscopic adrenalectomy (LA) demonstrated better perioperative outcomes, including lower estimated blood loss, lower hemodynamic instability (HDI) and shorter length of hospital stay without increasing complications [7].

Even for LA, intraoperative HDI, which is defined as hypertensive and hypotensive crises during anesthesia induction and tumor resection, remains a major concern for anesthesiologist and surgeons [8, 9]. Several factors have been reported to be associated with intraoperative HDI, including age [9], preoperative preparation [10], tumor size [8, 9], laterality [9], sarcopenia [8]. Our previous study had revealed that 24 h urinary output of urine vanillylmandelic acid (VMA) ≥ 58 μmol/day, tumor size ≥ 4 cm and Cluster 2 mutations were independent risk factors for HDI during surgery for pheochromocytoma and paraganglioma [8]. However, the cohort in our previous study consisted of both patients who underwent laparoscopic surgeries

and patients who underwent open surgeries. Besides, we failed to investigate the relationship between HDI and laterality. Studies focusing on risk factors associated with HDI during LA for PCCs solely are relatively few.

Recently, three-dimensional (3D) printing based on preoperative computed tomography (CT) have gained popularity, which can provide an anatomic understanding of the tumor from all angels and show the relationship between the tumor and the surrounding vessels and organs. It could aid surgeons in enacting a suitable surgical plan [11, 12]. Previous study has shown that 3D printing could decrease the fluctuations in blood pressure in laparoscopic surgery for PCCs [13]. However, the associations between the application of 3D printing and the risk of HDI during LA for PCCs still remains inconclusive. In this study, we retrospectively collected PCC cases who received LA from our center, aiming to (i) identify risk factors of HDI and develop a comprehensive model for individualized prediction of HDI during LA and (ii) investigate the relationship between 3D printing and HDI during LA.

Materials and methods

Patients

Consecutive patients with pathologically and surgically confirmed PCCs who underwent unilateral LA with curative intent were retrospectively collected at Xiangya Hospital, Central South University between January, 2010 and July, 2021. Exclusion criteria were the following: (1) laparoscopy that was converted to laparotomy during surgery (n=4); (2) coexistence of other tumors for surgery (n=2); (3) incomplete clinical data and genetic data (n=15); (4) missing preoperative CT images (n=15). Finally, 115 patients were included in this study. Our study was approved by the Medical Ethics Committee of our hospital (No. 202207152). Written informed consents were obtained from all patients.

Data collection

Demographic and clinical data were obtained through review of the medical records, including: gender, age at onset, preoperative body mass index (BMI), primary tumor location, primary tumor size, preoperative 24-h urinary output of VMA, preoperative baseline heart rate (HR), preoperative baseline systolic blood pressure (SBP) and diastolic blood pressure (DBP), intraoperative highest and lowest HR, SBP, and DBP and operation time.

CT scanning and 3D printing

Preoperative CT scans were performed with one of the three scanners: a 16-multi-detector CT (MDCT) (Brilliance 16, Philipps), a 64-MDCT (SOMATOM Definition, Siemens), and a 320-MDCT (Aquilion ONE, Toshiba Medical Systems). CT images were transferred to Digital Imaging and Communications in Medicine format. Medical Imaging Three Divisional Visualization System (Yorktal, Inc., Shenzhen, Guangdong, China) was applied to create 3D digital images after segmentation and reconstruction of CT images.

After modelling, the relationship between tumor and surrounding tissues can be easily distinguished by applying different colors to different structures like tumor, kidney, adrenal gland, arteries, and veins (**Figure 1**). The model would be uploaded to a cloud platform which surgeons can login in and access to the model and get a better visualization of the anatomy of the surgical area by rotating, zooming in or zooming out.

Treatments and definition

All patients received alpha-adrenergic blockade 1-2 weeks prior to surgery to normalize blood pressure. In patients with tachycardia, beta-blockade was applied after initiation of alpha-adrenergic blockade. Preoperative target value was defined as blood pressure less than 130/80 mmHg and a heart rate less than 90 beats/min. Transabdominal or retroperitoneal LA was performed by a team of skilled surgeons expertizing in adrenal surgery. Before surgery, standard general anesthesia was conducted and radial artery puncture and electrocardiograph was routinely performed. Blood pressure were recorded based on continuous intra-arterial measurement. The HR was recorded from the electrocardiogram. In our study, intraoperative HDI was defined as intraoperative SBP >180 mmHg and/or MAP <60 mmHg [8, 14-16].

Genetic tests

All patients in this study had received next-generation sequencing (NGS) using paraffin-embedded tumor specimens or frozen tumor

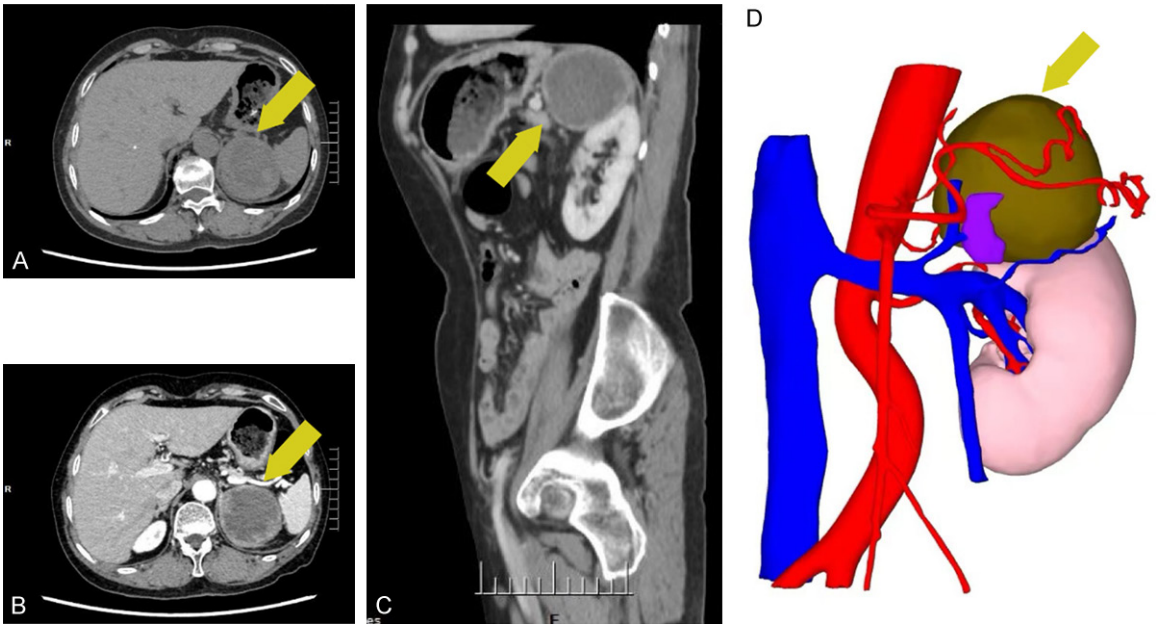

Figure 1. CT images and 3D printing model. A-C. A left-sided 6.5-cm pheochromocytoma in a 50-year-old man on CT scan. D. The corresponding 3D printing model. The tumor was indicated by yellow arrow.

tissues of PCCs for detection of mutations, which had been described in our previous study [3]. Customized NGS panel was applied which included *CSDE1, EGLN1, EPAS1, EGLN2, FGFR1, FH, HRAS, IDH1, SDHA, MDH2, NF1, RET, MAX, SDHB, SDHC, SDHD, SDHAF2, TMEM127* and *VHL* mutations. Patients with mutations in *EPAS1, EGLN1, EGLN2, FH, IDH1, MDH2, SDHA, SDHB, SDHC, SDHD, SDHAF2* and *VHL* belonged to the Cluster 1 group. Patients with mutations in *FGFR1, HRAS, MAX, NF1, RET* and *TMEM127* were classified as Cluster 2 group. Patients with mutation in *CSDE1* belonged to the Cluster 3 group.

Statistical analysis

All statistical analyses were performed by SPSS version 24.0 (IBM SPSS Inc., Chicago, IL, USA), and R software version 4.0.1 (http://www.r-project.org). Continuous variables with normal distribution were presented as mean (standard deviation) and tested by Student's *t*-test, and continuous non-normally distributed variables were presented as median (interquartile range) and tested by the Mann-Whitney *U* test. Categorical variables were compared using the Pearson chi-square test or Fisher's exact test. Univariate analysis and multivariate logistic regression analysis were performed to identify significant factors that were in association with HDI during LA. Variables with $P<0.05$ in univariate analysis were candidates for multivariate logistic regression analysis and remained in the model if they were still significantly associated with the results. These factors were used to build nomograms. The performance of the nomogram was evaluated respect to discrimination and calibration. The discrimination was represented by the area under the receiver operating characteristic (ROC) curve (AUC). The calibration of the nomogram was tested by plotting the observed outcome probabilities and predicted out probability using the logical model. A plot along the 45° line corresponds to a model in which the predicted outcome probabilities are identical with the observed outcome probabilities, indicating perfect calibration. A two-sided test $P<0.05$ was considered statistically significant.

Results

Patients' characteristics

A total of 119 patients were enrolled in the final study. All patients in the study were classified as having HDI (n=58) or hemodynamic stability (HDS) (n=61). Compared to patients with HDS, patients with HDI tended to have higher 24-h urinary outputs of VMA (65 vs 47.7 mg/day, $P=0.017$), harbor more right-sided tumors

Table 1. Patient characteristics

	Total (n=119)	HDI (n=58)	HDS (n=61)	*P*-value
Age (years), median (IQR)	47 (38-56)	48 (43-56)	45 (34-57)	0.232
Male, n (%)	57 (47.9%)	26 (44.8%)	31 (50.8%)	0.513
BMI (kg/m^2), mean (SD)	22.1 (3.3)	22.5 (3.7)	21.8 (2.9)	0.21
Tumour size (cm), median (IQR)	4.1 (3.3-5.1)	4.3 (3.5-5.2)	3.8 (3.1-5.0)	0.154
Incidentaloma, n (%)	22 (18.5%)	9 (15.5%)	13 (21.3)	0.416
Right adrenal, n (%)	78 (65.5%)	44 (75.9%)	34 (55.7%)	0.021
3D, n (%)	66 (55.5%)	22 (37.9%)	44 (72.1%)	<0.001
Cluster 2 mutation, n (%)	52 (43.7%)	33 (56.9%)	19 (31.1%)	0.005
Urine VMA (μmol/day), median (IQR)	56.2 (36.5-79.9)	65.0 (44.1-93.3)	47.7 (33.4-69.2)	0.017
Pre-anaesthetic blood pressure (mmHg), median (IQR)				
SBP	136 (120-156)	132 (123-160)	137 (119-151)	0.717
DBP	80 (73-90)	82 (74-90)	80 (70-90)	0.174
Pre-anaesthetic HR (b.p.m.), median (IQR)	80 (75-89)	83 (77-90)	79 (68-89)	0.041
Haemodynamic variables (mmHg), median (IQR)				
Maximum SBP	180 (160-200)	200 (190-223)	160 (139-175)	<0.001
Minimum SBP	104 (94-111)	104 (90-114)	103 (97-111)	0.496
ΔSBP	70 (50-98)	97 (84-116)	54 (39-66)	<0.001
Maximum DBP	100 (90-118)	112 (104-123)	90 (80-100)	<0.001
Minimum DBP	60 (58-70)	60 (54-70)	60 (60-70)	0.476
ΔDBP	40 (26-51)	51 (40-67)	28 (21-40)	<0.001
MAP	75 (70-83)	74 (67-84)	76 (72-83)	0.441
PP	78 (60-90)	89 (78-110)	62 (57-78)	<0.001
Intraoperative HR (b.p.m.), median (IQR)				
Maximum HR	99 (89-113)	104 (92-121)	90 (82-105)	0.001
Minimum HR	70 (62-80)	70 (63-80)	66 (62-76)	0.129
Length of surgery (min), median (IQR)	125 (95-160)	123 (100-156)	125 (90-163)	0.998

(75.9% vs 55.7%, *P*=0.021) and Cluster 2 mutations were more commonly detected in HDI patients (56.9% vs 31.1%, *P*=0.005) (**Table 1**). In our study, 66 patients underwent surgery after preoperative 3D printing. Less application of 3D printing was detected in patients with HDI (37.9% vs 72.1%, *P*<0.001).

For intraoperative hemodynamic parameters, maximal and fluctuating values for SBP and DBP in HDI patients were higher than those in HDS patients (*P*<0.001). Higher maximum HR were also recorded in patients with HDI (*P*<0.001). Age, gender, BMI, percentage of incidentaloma, pre-anaesthesia blood pressure did not differ significantly between patients with HDI and those with HDS. Characteristics of the patients were summarized in **Table 1**.

Univariate analysis and multivariate analysis

Univariate analysis revealed that 24 h urinary output of urine VMA (OR=3.356, 95% CI=1.582-7.120, *P*=0.001), tumor size (OR=2.393, 95% CI=1.141-5.018, *P*=0.02), right-side tumor location (OR=2.496, 95% CI=1.138-5.474, *P*=0.021), Cluster 2 mutations (OR=2.918, 95% CI=1.377-6.182, *P*=0.005) were potential risk factors for multivariate analysis (**Table 2**). Multivariate analysis showed that 24 h urinary output of urine VMA ≥ 58 μmol/day, tumor size ≥ 4 cm, right-side tumor location and Cluster 2 mutations were significant independent risk factors for HDI (**Table 2**). Multivariate analysis showed that preoperative 3D printing was an independent protective factor for HDI in patients with PCCs (OR=0.319, 95% CI=0.121-0.839, *P*=0.021) (**Table 2**).

Development of an individualized prediction nomogram

Prediction model 1 containing the clinical risk factors 24 h urinary output of urine VMA, tumor size and right-side tumor location was established and demonstrated an AUC of 0.721 (95%

Table 2. Univariate and multivariate analyses of significant factors for HDI during LA

	Univariate analysis			Multivariate analysis		
	OR	95% CI	P	OR	95% CI	P
Urine VMA ≥ 58 μmol/day	3.356	1.582-7.120	0.001	2.633	1.159-5.984	0.011
Tumour size ≥ 4 cm	2.393	1.141-5.018	0.02	3.129	1.305-7.505	0.011
Right side tumor location	2.496	1.138-5.474	0.021	3.721	1.458-9.496	0.006
Cluster 2 mutation	2.918	1.377-6.182	0.005	4.253	1.737-10.412	0.002
3D printing	0.236	0.109-0.511	<0.001	0.319	0.121-0.839	0.021

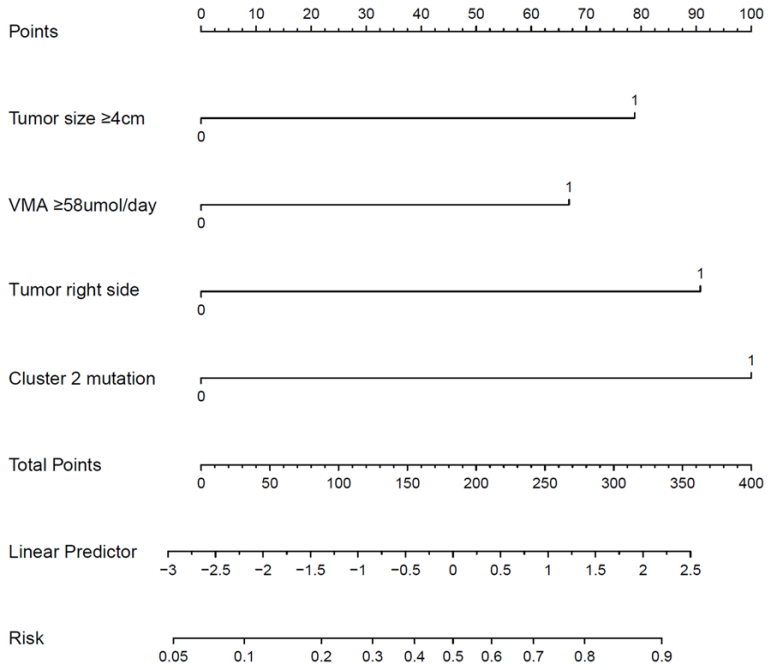

Figure 2. The nomogram based on risk factors.

CI, 0.629-0.813) with a sensitivity of 0.638 and a specificity of 0.705. The calibration curve showed a bias-corrected AUC of 0.702. Prediction model 2 containing the clinical risk factors and the cluster 2 mutations was established and demonstrated an AUC of 0.784 (95% CI, 0.701-0.867) with a sensitivity of 0.707 and a specificity of 0.787. The calibration curve showed a bias-corrected AUC of 0.758. Thus, model 2 was chosen as the final model and presented as a nomogram (**Figure 2**), indicating the importance of incorporating genetic features. The ROC and the calibration curve were presented in **Figure 3**.

Discussion

HDI is worthy of special attention as it has been revealed to be associated with increased risk of complications and morbidity during surgical resection of PCCs [17, 18]. Recent studies have revealed that LA does not increase the risk of HDI compared to open resection [7, 19]. For treating small to medium size PCCs, it has been widely accepted that LA is a safe procedure. For large PCCs, open resection was recommended at first in the 2014 guidelines of the Endocrine Society [20]. With improvement in laparoscopic techniques, the indication of LA has been extended to large PCCs currently [16, 21-23]. Therefore, LA has gradually became the first choice for PCCs resection. Thus, it is of urgent need to find features associated with HDI during LA. However, it still poses a clinical challenge to predict HDI during LA and studies related to risk factors of HDI during LA are lacking [6, 24]. Therefore, we aimed to identify factors related to HDI during LA and developed an easy-to-use and highly effective scoring model for predicting HDI during LA.

Our study revealed that 24 h urinary output of urine VMA ≥ 58 μmol/day, tumor size ≥ 4 cm, right-side tumor location, Cluster 2 mutations and 3D printing were associated with intraoperative hemodynamic during LA. 3D printing is an independent protective factor for HDI during LA and the rest four factors are independent risk factors for HDI. The identification of urine VMA, tumor size and cluster 2 mutations has validated the results of our previous study [8]. The nomogram based on four risk factors was developed for predicting risk of HDI.

Tumor size ≥ 4 cm was identified as a risk factor for HDI in our study, which was in accord with

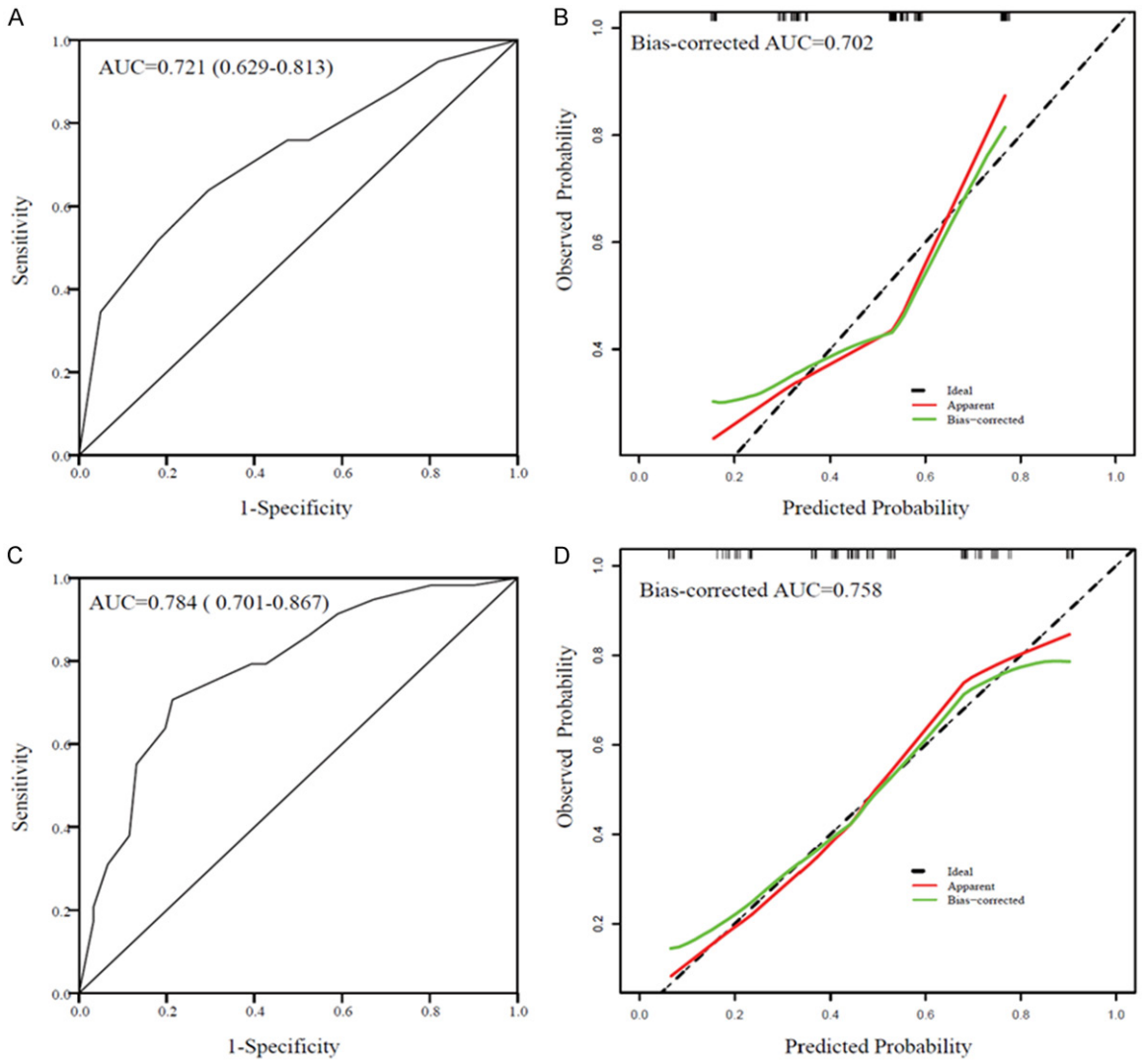

Figure 3. The value of the models to predict HDI during LA. A. Discrimination of the model 1. B. Calibration of the model 1. C. Discrimination of the model 2. D. Calibration of the model 2.

the results of other studies [6, 25, 26]. Considering that higher levels of catecholamines would be secreted by large PCCs, more episodes of hypertensive crisis may be encountered during LA for large PCCs. Besides, large tumor size may impose more pressure on surgeons due to the small operation space under endoscopy, which may require a longer manipulation time during tumor resection, resulting in subsequent catecholamine release and significant blood pressure fluctuation.

In our study, the PCCs on the right side tended to have a higher risk of HDI than the left-sided PCCs, which was in consistent with other study [9]. It has been reported that the right-sided LA is more difficult than the left-sided LA [27] due to anatomical factors such as the right suprarenal vein being shorter and more commonly variable [28]. Besides, the right-side tumors were larger and secreted higher levels of metanephrines [29].

Cluster 2 mutations were identified as independent risk factor for HDI during LA. The finding was in an agreement with previous studies focusing on associations between genetic mutations and different patterns of catecholamines secretion [8]. Tumors belonging to cluster 2 group express phenylethanolamine-N-methyltransferase, leading to epinephrine production. Thus, tumors with cluster 2 mutations usually harbor more storage of catecholamines compared with cluster 1 tumors that do

not produce considerable amounts of epinephrine [30]. Though tumors with cluster 2 mutations secrete catecholamines in a lower continuous manner compared with tumors with cluster 1 mutations, they can be more easily stimulated to secrete catecholamines [30, 31]. Thus, more episodes of secretion are thought to be detected in tumors with cluster 2 mutations than that of tumors with cluster 1 mutations [32]. Thus, it is no surprise that cluster 2 mutations could affect intraoperative HDI.

In our study, preoperative 3D printing is an independent protective factor for HDI during LA. With improvements in 3D printing technology, this application has gained wider acceptance. Compared to traditional CT images, 3D printing can provide a better anatomic understanding of the tumor area including the exact position of tumor and the relationship between the tumor and the surrounding blood vessels, important organs. During LA, it is important to ligate adrenal central vein as soon as possible to control bleeding and catecholamines secretion. With 3D printing in hand, surgeons can obtain the location of adrenal central vein prior to surgery and rapidly find and ligate it during surgery, which would prevent secretion of catecholamines into the bloodstream, thereby reducing blood pressure fluctuations and risk of developing heart failure and pulmonary edema [13, 33, 34].

Souzaki et al. used preoperative 3D-printed model for simulation of the laparoscopic view and the range of forceps movement prior to LA for adrenal neuroblastomas [34]. All tumors were completely resected without complications, indicating that 3D printing may be helpful for figuring out the surgical anatomy of the tumor and for planning surgical steps. Zhang et al. found that 3D printing is safe and feasible for patients undergoing laparoscopic surgery for pheochromocytoma and paraganglioma [13]. The application of 3D printing significantly reduced operation time and fluctuations in blood pressure.

There are other studies that have revealed risk factors for HDI during surgery for PCCs. Zhang et al. developed a nomogram consisting of seven predictors including age, tumor shape, Mayo Adhesive Probability score, laterality, necrosis, body mass index, and surgical technique [9]. The nomogram demonstrated an AUC of 0.739. However, the cohort in their study consisted of both patients who underwent open surgery and patients who underwent laparoscopic surgery. Huang et al. revealed that tumor size and previous hypertension history were risk factors for HDI during LA [6]. However, HDI was defined as intraoperative SBP above 160 mmHg in their study. In our study, we found that cluster 2 mutation was a new independent risk factor for HDI during LA. The model that incorporated the cluster 2 mutations also demonstrated a better AUC than the model without cluster 2 mutations, indicating the relationship between genetic mutations and hemodynamic response with PCC during LA.

There were several limitations in our study. As a single center retrospective study, selection bias could not be excluded. The sample size of our study was relatively small partly due to the exclusion of patients without genetic mutation data and preoperative CT images. Second, definitions of intraoperative HDI vary between studies, making the comparison of results difficult. Third, plasma or urinary catecholamines and metanephrines were not assessed preoperatively in our study, preventing us from exploring the relationship between catecholamines and HDI. Fourth, the nomogram in our study was developed without external validation. In the future, large-scale, multicenter studies are needed to validate the nomogram. Finally, preoperative CT scans were obtained from three different CT scanners, which may have effect on the subsequent 3D printing.

In conclusion, we identified several factors that were associated with HDI during LA for PCCs. Specifically, 24-h urinary output of VMA $\geq$ 58 μmol/day, tumor size $\geq$ 4 cm, right side tumor location and cluster 2 mutations were independent risk factors for HDI during LA and preoperative 3D printing was a protective factor for HDI during LA. The nomogram based on these four risk factors could be used as independent tool to evaluate individual patient's risk of developing HDI during LA, facilitating a better treatment strategy to reduce risk of complications and morbidity.

Acknowledgements

This work was supported by the Natural Science Foundation of Hunan Province (2022JJ40781). Author Xiao Guan has received research support from the Natural Science Foundation of Hunan Province.

Disclosure of conflict of interest

None.

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