Retrospective Cohort Study

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Genetic background and intraoperative haemodynamic instability in patients with pheochromocytoma and paraganglioma: a multicentre retrospective study

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Background: Perioperative management to maintain intraoperative haemodynamic stability is crucial during surgical treatment of pheochromocytomas and paragangliomas (PPGLs). Although ~70% of PPGLs carry pathogenic variants (PVs) in susceptibility genes, whether intraoperative haemodynamic instability (IHI) is associated with genetic background remains unclear. This study aimed to analyse IHI in patients with PPGL due to PVs in different genes.

Materials and Methods: This retrospective study recruited 756 patients with abdominal PPGL from two tertiary care centres. Clinical information including sex, age, catecholamine-associated signs and symptoms (CAS), tumour location and size, biochemistry, and perioperative characteristics were collected. Genetic mutations were investigated using next-generation sequencing.

Results: Among the 671 patients included in the analysis, 61.8% (415/671) had IHI. IHI was significantly associated with genetic background in patients with PPGL. Most (80.9%, 89/110) patients with PPGL due to PVs in *HRAS* suffered IHI. In contrast, only half (31/62) of patients with PPGL due to PVs in *VHL* had IHI. In the multivariate regression analysis, compared to those with negative genetic testing results, patients with PPGL due to PVs in *HRAS* (OR 3.82, 95% CI 2.187–6.679, $P < 0.001$), the other cluster 2 genes (OR 1.95, 95% CI 1.287–2. 569, $P < 0.05$), and cluster 1 genes other than *VHL* (OR 2.35, 95% CI 1.338–4.111, $P < 0.05$) were independent risk factors for IHI, while PVs in *VHL* was not independent risk factor (OR 1.09, 95% CI 0.605–1.953, $P \geq 0.05$). In addition, age at diagnosis of the primary tumour, presenting of CAS, and tumour size were identified as independent factors for IHI. The nomogram illustrated that genetic background as sharing the largest contribution to IHI, followed by tumour size, age, and presentation of CAS.

Conclusion: IHI is associated with the genetic background in patients with PPGL. The perioperative management of patients with PPGL can be personalised according to their genetic backgrounds, tumour size, age, and presentation of CAS.

Keywords: genetic background, intraoperative haemodynamic instability, paraganglioma, pheochromocytoma, pre-surgical treatment

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Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

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Introduction

Pheochromocytomas and paragangliomas (PPGLs) are rare neuroendocrine tumours characterised by the overproduction, storage, and secretion of catecholamines (dopamine, norepinephrine, and epinephrine)[1]. Approximately 60–70% of PPGLs carry germline or somatic pathogenic variants (PVs) in susceptibility genes, which are associated with four transcriptional pathways[2,3]. PPGLs due to PVs in genes that encode enzymes in the tricarboxylic acid cycle (TCA), including *SDHx*, *IHD2*, *FH*, *SUCLG2*, *MDH2* and *GOT2*, are characterised by activation of hypoxic pathways and are therefore classified as pseudohypoxic clusters (cluster 1A)[4]. Another pseudohypoxic cluster (cluster 1B) has been associated with PVs in genes such as *VHL*, *PHD1/2*, and *EPAS1*[4]. PVs in genes such as *RET*, *NF1*, *HRAS*, *FGFR1*, *TMEM127* and *MAX* cause the activation of kinase signalling pathways and are therefore classified as kinase clusters (cluster 2)[4]. In addition to these well-established clusters, a few cases with mutations in *CSDE1* or *MAMAL3* fusion gene resulting in activation of the Wnt pathway have been identified (cluster 3)[5].

Non-metastatic PPGLs can generally be cured by surgical resection; however, this treatment strategy has been associated with significant morbidity. Surgical morbidity is largely attributed to intraoperative haemodynamic instability (IHI), hypertension crisis caused by hypersecretion of tumoral catecholamines into the streaming blood and vasodilation caused by tumour devascularization[6]. In the very early stages of this surgery, before the introduction of α-adrenoceptor blockade, the mortality rate of PPGL operation was ~25% or higher[7]. Perioperative treatment with α-adrenoceptor blockade substantially decreased peri-surgical mortality[8,9]. However, the morbidity rates remain high, with incidences ranging from 10.7 to 29.8% with qualified perioperative preparations[10–12]. In addition, controversies regarding α-adrenoceptor blockade have recently arisen, as treatment with α-adrenoceptor blockade is not sufficient to avoid IHI in many patients[13–16]. Besides, in some patients, pre-surgical treatment with α-adrenoceptor blockade is not necessary or even harmful[17]. Not all patients with PPGL require pre-surgical treatment with α-adrenoceptor blockade to avoid catecholamine-associated IHI. However, there is no clear indicator of how to stratify patients.

HIGHLIGHTS

- Patients with PPGL due to pathogenic variants in different genes showed distinguished intraoperative haemodynamic characteristics.
- Genetic background, age at diagnosis of the primary tumour, tumour size and presentation of CAS were independent predictors of IHI in patients with PPGL.
- A predictive nomogram for the risk of IHI in patients with PPGL was built, which showed that genetic background as sharing the largest contribution to IHI, followed by tumour size, age and presentation of CAS.

Recent studies have revealed that catecholamine biosynthesis, storage, and secretion by PPGLs are regulated by genetic background[18]. In addition, a previous study by our group showed that more patients with PVs in cluster 2 developed IHI than those without PVs in known susceptibility genes[6]. These results indicate that genetic background may affect IHI through the regulation of catecholamine metabolism. Therefore, this study, with a large PPGL cohort recruited from two centres, aimed to investigate IHI in patients with PPGL due to PVs in different genes. Moreover, clinical characteristics that are associated with IHI will be analysed for individualised pre-surgical preparation of patients with PPGL.

Materials and methods

Study design and participants

This study included retrospective data from 756 patients with abdominal PPGL treated between 1 January 2009 and 31 July 2022 at two tertiary Chinese medical centres (Xiangya Hospital, Central South University and Zhongshan Hospital, Fudan University). All patients with a pathologically confirmed diagnosis of PPGL were surgically treated, as previously reported[2,19,20]. Among these patients, 42 were excluded because of a lack of genetic testing results, while 43 were excluded because of the unknown significance of the identified variant (Fig. 1). This study

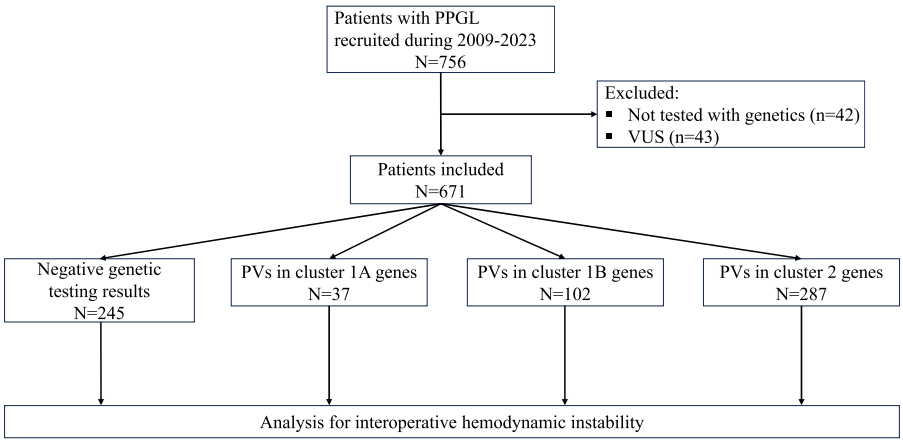

Figure 1. Flow-through chart of patient inclusion and exclusion. PPGL, pheochromocytoma and paraganglioma; PVs, pathogenic variants; VUS, variant of unknown significance.

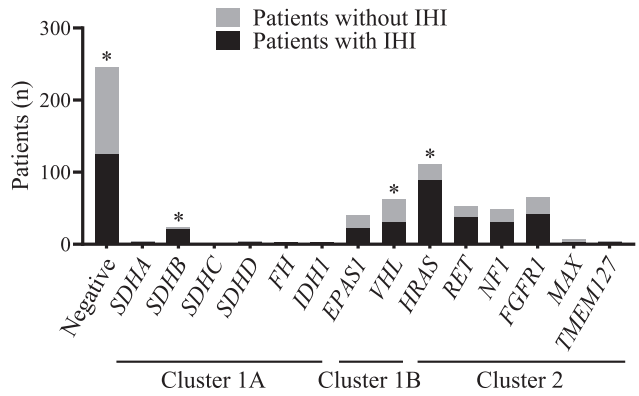

Figure 2. Proportion of intraoperative haemodynamic instability in patients with PPGL due to different genetic backgrounds. The proportion of intraoperative haemodynamic instability (IHI) in patients with PPGL was significantly associated with genetic backgrounds, with significant differences in patients with PPGL due to PVs in *SDHB*, *VHL* and *HRAS*, and those without PVs. *$P < 0.05$.

was registered in the Chinese Clinical Trial Registry (No. ChiCTR2100050937). In addition, 312 patients were recruited from Zhongshan Hospital, Fudan University. All patients were recruited using the study protocols approved by the ethics committee of each participating hospital. Written informed consent for genetic analysis was obtained from all patients. This work has been reported in line with the STROCSS criteria[21], Supplemental Digital Content 1, http://links.lww.com/JS9/D242.

Data collection and definition

We collected data on age at diagnosis, sex, the reason for referral, presence of catecholamine-associated symptoms, hypertension, tumour size and location, 24-h urinary vanillylmandelic acid (VMA), plasma normetanephrine and metanephrine levels, premedication status, surgical approach, and intraoperative blood pressure (BP). All data were retrieved from the electronic medical records of both centres. Intraoperative haemodynamic instability was defined as a maximum systolic BP ≥ 180 mmHg and/or mean artery pressure ≤ 60 mmHg, as defined in studies[6,22–24]. Supplementary Figure S1 (Supplemental Digital Content 2, http://links.lww.com/JS9/D243) is a diagram that shows the actual situation of IHI in a patient with pheochromocytoma (Supplementary Fig. 1, Supplemental Digital Content 2, http://links.lww.com/JS9/D243). Hypertension was defined as a systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg or a known history of hypertension and already on antihypertensive medication. Catecholamine-associated signs and symptoms (CAS) were defined as presenting hypertension, headache, diaphoresis, palpitations, tremor, pallor, panic, nausea and classic triad, as previously described[2,5].

Genetic testing

Details of testing for PVs in PPGL-associated genes have been described previously. Briefly, genetic testing was performed using next-generation sequencing (NGS) with DNA isolated from paraffin-embedded tumour specimens or frozen tumour tissue, as previously described[2,19,20]. All genetic tests were performed using a customised NGS panel that included *SDHA*, *SDHB*, *SDHC*, *SDHD*, *SDHAF2*, *VHL*, *EPAS1*, *EGLN1*, *EGLN2*, *IDH1*, *FH*, *MDH2*, *NF1*, *MAX*, *RET*, *TMEM127*, *FGFR1*, *HRAS*, and *CSDE1*. PVs in these genes were confirmed by Sanger sequencing.

Statistical analysis

Non-normally distributed continuous data were displayed as medians and interquartile ranges (IQR). Categorical data were expressed as numbers (%). The Mann–Whitney *U* test was used

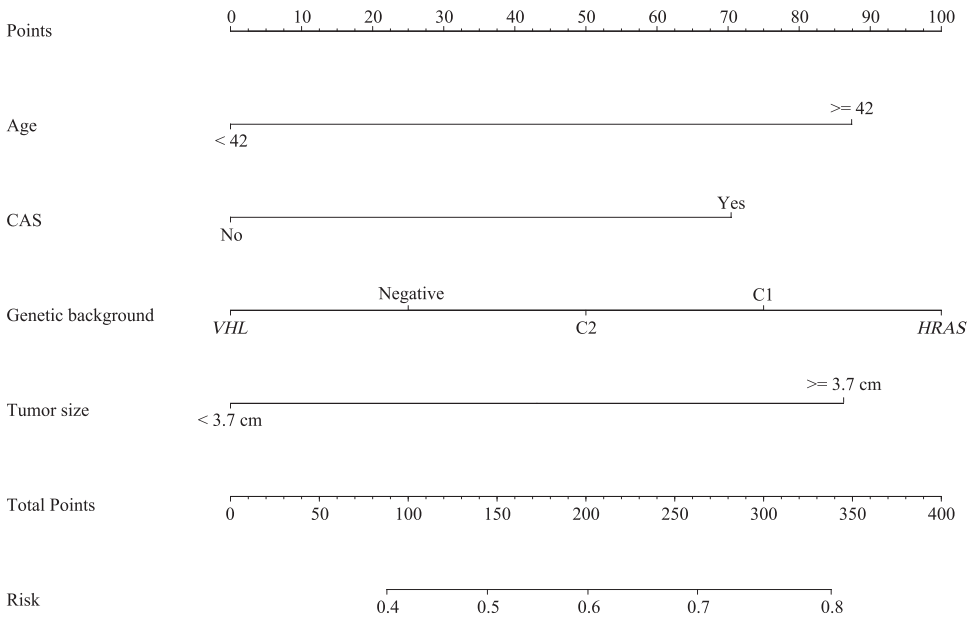

Figure 3. Nomogram for predicting IHI in patients with PPGL. Each value is located on a variable axis, and a line is drawn upward to determine the points for each variable value. The sum of these numbers is located on the total points axis, and a line is drawn downward to the survival axes to determine the probability of developing IHI in patients with PPGL. CAS, catecholamine associated signs and symptoms; C1, cluster 1; C2, cluster 2.

to compare non-normally distributed continuous data. Differences in frequencies were tested using the χ^2 test or Fisher's exact test. Binary logistic regression was applied to identify variables related to the IHI. For variables that were significantly different in the univariate analysis, multivariate logistic regression analysis was performed to identify independent factors affecting IHI. The ROC curve was used to determine the cut-off values for continuous variables at the largest Youden index (Youden index = [sensitivity + specificity] – 1). Odds ratios (ORs) and 95% confidence intervals (CI) are presented. Statistical significance was defined as $P < 0.05$. All statistical analyses were performed using SPSS software (version 25.0; SPSS Inc., Chicago, Illinois, USA).

Results

Clinical characteristics

In total, 671 patients were included in the analysis (Fig. 1). The patients, including 340 males and 331 females, were diagnosed with PPGL at a median age of 49 (IQR, 39–57) years (Supplementary Table S1, Supplemental Digital Content 2, http://links.lww.com/JS9/D243). Among the 671 patients, 415 (61.8%) developed IHI while 256 did not. Overall, 245 (36.5%) patients did not have PVs in known susceptibility genes, 37 (5.5%) had PVs in cluster 1A genes, 102 (15.2%) had PVs in cluster 1B genes, and 287 (42.8%) had PVs in cluster 2 genes (Fig. 1). Among all the patients, 452 (67.4%) presented with CAS. A proportion of 40.1% (261/451) of the patients were referred to the hospital for incidental identification of PPGL. A total of 88.3% (414/469) of the patients with PPGL were biochemically positive before surgery, either by testing for 24 h VMA (225/261), plasma metanephrine and normetanephrine (187/206), or both (2/2). Furthermore, 521 patients (77.6%) were treated with α-adrenoreceptor blockade before surgery (Supplementary Table S1, Supplemental Digital Content 2, http://links.lww.com/JS9/D243).

IHI in patients with PPGL due to PVs in different genes

Patients with PPGL from different genetic backgrounds showed distinct intraoperative haemodynamic characteristics (Fig. 2). Approximately half of the patients (120/245) with negative genetic test results did not develop IHI. Among the 37 patients with PPGL caused by PVs in cluster 1A, 83.8% had IHI, which was mainly associated with a relatively high proportion of patients with PPGL due to PVs in *SDHB* who suffered IHI (87%, 20/23). In patients with PPGL due to PVs in cluster 1B genes, half (31/62) of those with *VHL* and 55% (22/40) of those with *EPAS1* PVs suffered IHI. In addition, 71.8% (206/287) of the patients with PVs in cluster 2 had IHI. Among these patients, most (80.9%, 89/110) with PPGL due to PVs in *HRAS* suffered IHI. Approximately 71.7% (38/53) of patients with PPGL due to PVs in *RET* had IHI. The proportions of IHI in patients with PPGL due to PVs in *NF1* and *FGFR1* were 63.3% (31/49) and 64.2% (42/65), respectively (Fig. 2).

Clinical and genetic features associated with IHI in patients with PPGL

Patients with IHI were significantly older than those without IHI [49 (IQR 41–58) years vs. 47 (IQR 36–56) years, $P = 0.011$] (Table 1). Compared with those without CAS, more patients with CAS experienced IHI (71.6 vs. 60.5%, $P = 0.003$). Consequently, compared to those who were referred to the hospital because of signs and symptoms, fewer patients with incidentaloma had IHI (36.6 vs. 42.6%, $P = 0.044$). Patients who suffered IHI had a higher urine VMA than those who did not suffer IHI [68 μmol/day (IQR 42.9–116.9) vs. 51 μmol/day (IQR 33.6–102.3), $P = 0.004$], while the proportion of positive biochemical testing results showed no significant difference between patients. As previously mentioned, the distribution of genetic mutations among those who suffered IHI was significantly different from patients without IHI ($P < 0.001$). As expected, more patients with IHI were transferred to the intensive care unit (ICU) directly after surgery (43.6 vs. 21.1%, $P < 0.001$). The proportion of patients

Table 1

Clinical characteristics of patients with and without intraoperative haemodynamic instability.

	Intraoperative haemodynamic instability		*P*
Patient	Yes ($n = 415$)	No ($n = 256$)	
Age, median (IQR)	49 (41–58)	47 (36–56)	0.011
Sex (male), %	50.4% (209/415)	51.2% (131/256)	0.838
CAS, %	71.6% (297/415)	60.5% (155/256)	0.003
Incidentaloma, %	36.6% (152/415)	42.6% (109/256)	0.044
Tumour location, %			0.456
Adrenal	73% (303/415)	77.3% (198/256)	
Extra-adrenal	25.5% (106/415)	21.9% (56/256)	
Adrenal and extra-adrenal	0.5 (2/415)	0.4% (1/256)	
Biochemical positive[a], %	89.4% (271/303)	86.1% (143/166)	0.289
24 h urine VMA (μmol), median (IQR)	68 (42.9–116.9)	51 (33.6–102.3)	0.004
Plasma NMN (nmol/l), median (IQR)	5.9 (2–14)	7 (2–15.9)	0.463
Plasma MN (nmol/l), median (IQR)	0.5 (0.2–1.9)	0.6 (0.2–1.8)	0.449
α-adrenoceptor blockade usage, %	80% (332/415)	73.8% (189/256)	0.062
Tumour size (cm), median (IQR)	4.4 (3.3–5.9)	4.2 (3–5.7)	0.049
Surgical approaches, %			0.363
Minimally invasive	54.2% (225/415)	57.8% (148/256)	
Open	45.8% (190/415)	42.2% (108/256)	
Estimated blood loss (ml), median (IQR)	150 (50–400)	200 (50–400)	0.236
Intravenous fluids infusion	2000 (1500–2500)	2500 (2000–3250)	< 0.001
Blood products infusion	16% (41/256)	26.3% (109/414)	0.002
Duration of the operation (min), median (IQR)	120 (90–150)	127 (92–178)	0.025
ICU stay, %	43.6% (181/415)	21.1% (54/256)	< 0.001
Post-operative hospital stay (day), median (IQR)	6 (5–8)	6 (5–7)	0.667
Genetic background, %			< 0.001
Negative	51% (125/245)	49% (120/245)	
Cluster 1A	83.8% (31/37)	16.2% (6/37)	
Cluster 1B	52% (53/102)	48% (49/102)	
EPAS1	55% (22/40)	45% (18/40)	
VHL	50% (31/62)	50% (31/62)	
Cluster 2	71.8% (206/287)	28.2 (81/287)	
HRAS	80.9% (89/110)	19.1% (21/110)	
The other cluster 2	66.1% (117/177)	33.9% (60/177)	

CAS, catecholamine-associated signs and symptoms; IQR, interquartile range; MN, metanephrine; NMN, normetanephrine; VMA, vanillylmandelic acid.

[a]Testing of 24 h urine VMA and plasma metanephrine or normetanephrine were performed in 263 and 208 patients, respectively.

Table 2

Univariable and multivariable logistic regression of factors associated with IHI in patients with pheochromocytomas and paragangliomas.

	Univariable	Multivariable
Age (≥ 42 years)	1.77 (1.266–2.479)**	1.73 (1.199–2.494)*
Incidentaloma	0.82 (0.592–1.125)	
Tumour size (≥ 3.7 cm)	1.61 (1.163–2.237)*	1.64 (1.162–2.311)*
CAS	1.64 (1.180–2.279)*	1.55 (1.093–2.200)*
Genetic background (refer to negative)		
Cluster 1		
VHL	0.96 (0.550–1.676)	1.09 (0.605–1.953)
The other cluster 1	2.12 (1.231–3.650)*	2.35 (1.338–4.111)*
Cluster 2		
HRAS	4.07 (2.377–6.964)**	3.82 (2.187–6.679)**
The other cluster 2	1.87 (1.255–2.791)*	1.95 (1.287–2.956)*

*$P < 0.05$.
**$P < 0.001$.
Results were presented as OR (95% CI).
CAS, catecholamine associated signs and symptoms.

treated with α-adrenoreceptor blockade before surgery was not significantly different between those treated with and without IHI. There were no differences in sex distribution, tumour size and location, or surgical approach between patients with and without IHI (Table 1).

Risk factors of IHI in patients with PPGL

Univariate and multivariate logistic regression analyses were performed to investigate factors independently associated with IHI among patients with PPGL. In univariate logistic regression, age at diagnosis of the primary tumour, presence of CAS, tumour size and genetic background were identified as factors associated with IHI in patients with PPGL (Table 2). Multivariate logistic regression identified that tumour size ≥ 3.7 cm (OR 1.61, 95% CI 1.162–2.311, $P < 0.05$), age at diagnosis of the primary tumour ≥ 42 years old (OR 1.73, 95% CI 1.199–2.494, $P < 0.05$), and presenting of CAS (OR 1.55, 95% CI 1.093–2.200, $P < 0.05$) as independent factors for predicting IHI (Table 2). In addition, compared to those with negative genetic testing results, PVs in cluster 2 gene *HRAS* (OR 3.82, 95% CI 2.187–6.679, $P < 0.001$), the other cluster 2 genes (OR 1.95, 95% CI 1.287–2. 569, $P < 0.05$), and cluster 1 genes other than *VHL* (OR 2.35, 95% CI 1.338–4.111, $P < 0.05$) were independent risk factors for IHI, while PVs in *VHL* was not independent risk factor (OR 1.09, 95% CI 0.605–1.953, $P \geq 0.05$) (Table 2).

Predictive nomogram for the risk of IHI in patients with PPGL

The nomogram that integrated all the variables selected by multivariate logistic regression was created for individualised management of PPGL (Fig. 3). The nomogram illustrated genetic background as sharing the largest contribution to developing IHI in patients with PPGL, followed by age at diagnosis of the primary tumour, tumour size and presenting of CAS. Based on the contribution to IHI, each variable was assigned a score on the point scale. Adding up the scores related to each variable and projecting total scores to the bottom scales, we can easily draw a straight line down to determine the estimated probability of developing IHI in patients with PPGL.

Discussion

IHI of patients with PPGLs has been a clinical dilemma since the introduction of surgical treatment for these rare tumours. In the present study, we found that intraoperative haemodynamic characteristics were associated with genetic background. More importantly, we showed that the genetic background, age at diagnosis of the primary tumour, tumour size and presentation of CAS were independent predictors of IHI in patients with PPGL. This study paves the way for the individualised perioperative management of patients with PPGL.

PPGLs caused by PVs in different genes have distinct catecholamine metabolism characteristics[18,26–28]. A study by Li. *et al*., which involved the investigation of a large clinical cohort and experimental analysis in a genetically modified cell line with *HRAS* PVs, indicated that *HRAS* increased epinephrine and dopamine biosynthesis, which led to a higher catecholamine content in these tumours than in PPGLs due to PVs in cluster 1 genes[29]. This partly explains the higher incidence of IHI in patients with tumour due to PVs in *HRAS* in the present study. Conversely, it has been reported that secretory pathways were more dysregulated in PPGLs due to PVs in *VHL* than in cluster 2 gene *RET*, which can result in a more continuous than episodic secretion of catecholamines in tumours due to PVs in *VHL*[30]. As a result, fewer catecholamines are stored in PPGLs due to PVs in *VHL* than in cluster 2 gene *RET*. This genetic–catecholamine metabolism association explains the significantly higher risk of IHI in patients with PPGL due to PVs in *HRAS*.

On the other hand, our study indicated that patients with PPGL due to PVs in *VHL* had the lowest risk of IHI, especially those without CAS. In a registry of patients with PVs in *VHL*, 65% of those with confirmed PPGL and 95% of patients with suspected PPGL were clinically silent[31]. In addition, a recent study indicated that 59.0% (69/117) of patients with normotensive PPGL had no IHI. These studies are consistent with our finding that only 30% (6/20) of patients with clinically silent PPGL due to PVs in *VHL* experienced IHI during surgery. All these indicated the importance of individualised preoperative preparatory strategies based on genetic background catecholamine physiology and PPGL secretory profile.

The perioperative mortality rate regarding the surgical treatment for PPGLs can reach up to 25% at a very early stage[7]. The introduction of preoperative treatment with α-adrenoreceptor blockade has dramatically decreased perioperative mortality and morbidity[8,9]. Therefore, pre-surgical preparation with α-adrenoreceptors blockade is recommended as a standard treatment for patients with PPGL in many guidelines[32,33]. However, some recent retrospective studies have indicated that pre-surgical treatment with α-adrenoreceptors blockade is useful but not sufficient to avoid IHI in some patients with PPGL[34]. Conversely, a prospective study investigating selectively normotensive patients with pheochromocytoma indicated that the use of α-adrenoreceptors blockade brings no benefits to intraoperative haemodynamic stability while increasing the usage of vasoactive drugs[17]. These results indicate that an individualised pre-surgical preparation strategy for preventing IHI is imperative in the surgical treatment of PPGLs. This study, based on a large cohort, indicated that genetic background, age at diagnosis of the primary tumour, tumour size, and the presence of CAS are independent factors associated with IHI.

After that, a predictive nomogram for the risk of IHI in patients with PPGL was developed based on these risk factors. Therefore, we suggest that individualised preoperative management strategies for patients with PPGL could be developed based on this nomogram. For example, a prolonged pre-surgical preparation of more than 2 weeks should be applied for those with a high risk of IHI. In addition, medications other than α-adrenoceptor blockade such as calcium channel blockers and metyrosine, might be alternatives or additional medication[35,36].

The identification of germline PVs in patients with PPGL before surgery is easily accessible and recommended for all patients with PPGL[32]. This may serve as a valuable tool for subsequent clinical decision-making regarding the prevention of IHI in these patients. However, testing for somatic PVs in tumours before surgery is challenging. With regard to clinical parameters, our group previously reported that predicting genetic background is feasible in patients with PPGL[37], which has also been reported by Baechle *et al*.[38]. However, it has also been reported that genetic backgrounds can be predicted by pre-surgical radiomics in many tumours[39–41]. These results indicate that artificial intelligence could help predict somatic PVs in PPGLs before surgery, and may serve as a useful tool for the clinical management of these patients.

This study has several limitations which should be discussed. Firstly, the retrospective nature of this study may have introduced confounder bias, recall bias, selective bias, and misclassifications. Second, only a small number of patients were tested for germline mutations, which limited the analysis of IHI in patients with PPGL owing to potential differences in hereditary backgrounds. Third, among the patients who underwent biochemical testing, approximately half were tested for urine VMA, whereas the other half were tested for plasma metanephrine and normetanephrine, which limited the correlation of genetic variants, biochemistries, and intraoperative haemodynamic characteristics. Nevertheless, our study included comprehensive clinical data, intraoperative haemodynamic parameters, and genetic test results from a large PPGL cohort recruited from multiple centres, which led to solid conclusions.

In conclusion, this study reported that the prevalence of IHI in patients with PPGL is associated with their genetic background. More importantly, we showed that genetic background and the presence of CAS were independent risk factors for IHI in patients with PPGL. Our study indicates that the perioperative management of patients with PPGL should be based on genetic background in addition to the presenting signs and symptoms.

Ethical approval

All patients were recruited using the study protocols approved by the ethics committee of Xiangya Hospital (No. 202106109) and Zhongshan Hospital (B2019-007R).

Consent

Written informed consent was obtained from the patient for publication and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

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Author contribution

M.L., L.L., and J.J.: study concept and design; Y.P., Y.H., Y.S., J.W., X.X., J.L., K.C., Z.L., Y.L., and X.G.: data collection; M.L., J.Z., L.L., and J.J.: data analysis and interpretation; M.L. and J. Z.: writing the manuscript; G.E., L.L., and J.J.: critical review of the manuscript.

Conflicts of interest disclosure

All of the authors have disclosed no conflicts of interest.

Research registration unique identifying number (UIN)

This study was registered in the Chinese Clinical Trial Registry (No. ChiCTR2100050937).

Guarantor

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Data availability statement

Data are available upon reasonable request.

Provenance and peer review

Not commissioned, external peer-review.

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