Impact of body composition and genotype on haemodynamics during surgery for pheochromocytoma and paraganglioma

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Abstract

Background  Maintaining intraoperative haemodynamic stability can reduce cardiovascular complications during surgery for pheochromocytoma and paraganglioma (PPGL). Risk factors such as tumour size and catecholamine levels are reported to predict haemodynamic responses during surgery for PPGL. We hypothesized that additional factors including body composition and genetic information could further improve prediction.

Methods  Consecutive patients with PPGL confirmed by surgical pathology between June 2010 and June 2019 were retrospectively included. Cross-sectional computed tomography images at the L3 level were used to assess body composition parameters including skeletal muscle area and visceral fat area. Next-generation sequencing was performed using a panel containing susceptibility genes of PPGL. Differences in clinical-genetic characteristics and body composition parameters were analysed and compared in patients with and without intraoperative haemodynamic instability (HDI).

Results  We included 221 patients with PPGL (median age 47 [38–56] years, and 52% male). Among them, 49.8% had Cluster 2 mutations (related to kinase signalling pathways), 44.8% had sarcopenia, and 52.9% experienced intraoperative HDI. Compared with patients without HDI, more patients with HDI had Cluster 2 mutations (59.8% vs. 38.5%, P = 0.002) and less had sarcopenia (35.9% vs. 54.8%, P = 0.005). Multivariate analysis showed that urine vanillylmandelic acid ≥ 58 μmol/day (adjusted odds ratio [OR] = 1.840, 95% confidence interval [CI] = 1.012–3.347, P = 0.046), tumour size ≥ 4 cm (adjusted OR = 2.278, 95% CI = 1.242–4.180, P = 0.008), and Cluster 2 mutations (adjusted OR = 2.199, 95% CI = 1.128–4.285, P = 0.021) were independent risk factors for intraoperative HDI, while sarcopenia (adjusted OR = 0.475, 95% CI = 0.266–0.846, P = 0.012) decreased the risk.

Conclusions  Body composition and genotype were associated with intraoperative haemodynamics in patients with PPGL. Our results indicated that inclusion of body composition and genotype in the overall assessment of patients with PPGL helped to predict HDI during surgery, which could assist in implementing preoperative and intraoperative measures to reduce perioperative complications.

Keywords  Pheochromocytoma; Paraganglioma; Haemodynamic instability; Sarcopenia; Gene mutations; Risk factors

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**Introduction**

Pheochromocytoma (PCC) and paraganglioma (PGL), commonly denoted as PPGL, are neuroendocrine tumours arising from chromaffin cells of the adrenal medulla or extra-adrenal neural crest progenitor cells. The incidence of PPGL has increased mainly due to improved detection on imaging over the past two decades. PPGL tumours can secrete excessive amounts of catecholamines and may cause endocrine hypertension and haemodynamic instability (HDI). HDI was defined as hypertension during anaesthesia induction and tumour resection, as well as severe post-operative hypotension. Preventive measures, such as adequate preoperative preparation, and modification of anaesthesia and surgical techniques, have decreased perioperative mortality in patients with PPGL. However, the incidence of intraoperative HDI remains as high as 31.3% and the incidence of cardiovascular complications remains at 5%.

For optimal surgical outcomes in patients with PPGL, it may be useful to preoperatively identify the risk factors for intraoperative HDI and thereby take appropriate measures to decrease the risk of perioperative complications. Several factors associated with intraoperative HDI have been reported for patients with PPGL, including preoperative preparation, concomitant diseases, tumour size, catecholamine levels, preoperative antihypertensive drugs, surgical procedures, and the use of crystal/colloidal fluids preoperatively. This information has been helpful to improve the understanding and management of intraoperative HDI, but other factors such as sarcopenia and the underlying genetic mutations responsible for PPGLs should also be assessed.

Sarcopenia, as defined as low levels of muscle strength, muscle quantity/quality, and physical performance, represents another factor that might impact HDI. Visceral obesity may also impact HDI. For example, sarcopenia has been shown to affect haemodynamics in patients with chronic disorders, such as diabetes and vascular disease, while visceral obesity can impact haemodynamics in otherwise normal individuals. Among these studies, it has been shown that abdominal visceral obesity is associated with blunted alterations in systolic blood pressure (SBP) and mean arterial pressure (MAP), which may be related to decreased cardiovascular reactivity. Another study showed that the visceral fat area was negatively correlated with left ventricular ejection fraction, thus affecting haemodynamics, especially SBP. While these studies raise the possibility that body composition may impact intraoperative haemodynamics in patients with PPGL, this presently remains unknown.

Pathogenic genetic mutations are an important cause of PPGL. These mutations mainly include two clusters: the cluster related to pseudo-hypoxia pathways (Cluster 1 mutations) and the cluster related to kinase signalling pathways (Cluster 2 mutations). These two clusters of genetic mutations underlying PPGL are different in synthesis, metabolism, and secretion of the catecholamines. PPGL with Cluster 1 mutations mainly have a noradrenergic phenotype, while PPGL with Cluster 2 mutations mainly have an adrenergic phenotype. The differences in catecholamines between the two clusters may contribute to different haemodynamic responses during surgery. Catecholamine levels such as urinary epinephrine have been reported as a risk factor for HDI during surgery. Therefore, the underlying genotype of the tumour is closely associated with catecholamines, which may help to predict the risk for intraoperative haemodynamic complications in patients with PPGL.

In this study, we retrospectively analysed clinical data, body composition parameters, and genetic information for a cohort of patients with PPGL, aiming to identify potential risk factors for intraoperative instability. Body composition parameters including skeletal muscle area and visceral fat area and subcutaneous fat area were assessed on cross-sectional computed tomography (CT) images at the third lumbar vertebra (L3) level. The clinical data, body composition parameters, and genetic information were evaluated for patients with haemodynamic stability (HDS) and those with HDI.

**Methods**

**Patients**

Consecutive patients with PPGL confirmed by surgical pathology in our hospital between June 2010 and June 2019 were retrospectively included (n = 402) (Figure 1). Exclusion criteria were the following: (a) coexistence of other tumours for surgery (n = 3); (b) bladder PGL followed by transurethral resection of the bladder tumour (n = 9); (c) head and neck PGL tumours, which secrete almost no catecholamines (n = 65); (d) recurrent and bilateral PPGL (n = 10); (e) missing preoperative CT or suboptimal CT images (n = 85); (f) laparoscopy that was converted to laparotomy during surgery (n = 4); and (g) patients with unknown gene mutation status (n = 5). There were no statistical differences in age, gender, tumour type, tumour size, incidentaloma, or use of alpha-adrenergic blockade between the included patients and excluded patients (Supporting Information, Table S1). Our study was approved by the Medical Ethics Committee in our hospital (No. 202106109) and was registered at Chinese Clinical Trial Registry (No. ChiCTR2100050937).

**Data collection**

Demographic and clinical data were obtained through medical record review, including the following: body mass index (BMI), tumour type, tumour size (mean diameter), preoperative...
tive 24-h urinary output of vanillylmandelic acid (VMA), premedication status, comorbidities, pre-anaesthesia blood pressure and heart rate (HR), surgical methods, intraoperative blood pressure and HR, intraoperative intake (crystal fluids, colloidal fluids, blood products, cardiovascular drugs, etc.), length of surgery (from first incision to suture wound closure), post-operative intensive care unit (ICU) admission, post-operative hospital stays (from the operation date to the discharge date), and post-operative complications.

**Treatments and definition**

All patients with PPGL underwent standard preoperative preparation and haemodynamic management. All patients with a diagnosis or suspected diagnosis of PPGL received alpha-adrenergic blockade 1–2 weeks prior to surgery to control blood pressure, while patients without a suspected diagnosis of PPGL did not receive alpha-adrenergic blockade before surgery. In addition, patients with higher HR received beta-adrenergic blockade before surgery. Preoperative target values were SBP/diastolic blood pressure (DBP) < 130/80 mmHg and HR < 90 b.p.m. Antihypertensive drugs were also used in patients who could not achieve targeted blood pressure with blockers. The surgical approach was laparoscopic (transabdominal or retroperitoneal) or open, both of which were performed by a team of skilled surgeons who avoided deliberately touching or squeezing the tumours during surgery. Blood pressure during surgery was monitored by continuous intra-arterial measurement. Before surgery, all patients underwent radial artery puncture and electrocardiograph monitoring. Based on real-time monitoring data, blood pressure and HR were recorded every 5 min. The recorded values in line plot delineated trends in blood pressure and HR, allowing us to capture extreme values of SBP, DBP, and HR during surgery.

In this study, intraoperative HDI in patients with PPGL was defined as intraoperative SBP > 180 mmHg and/or MAP < 60 mmHg. Using this definition, patients with PPGL were categorized as having HDI or HDS. The cut-off values for urine VMA of ≥58 μmol/day and tumour size of ≥4 cm were determined by receiver operating characteristic (ROC) curve analysis (Figure S1). Post-operative complications were classified by Dindo–Clavien classification.

**Pathological re-assessment and genetic sequencing**

Haematoxylin–eosin-stained and immunohistochemistry-stained tumour sections were independently re-assessed by two pathologists specializing in adrenal tumours. (J. W. and...
B. X., with 11 and 10 years of experience, respectively) for confirmation of PCC/PGL diagnosis. When necessary, the paraffin-embedded tumour tissue was re-sectioned and re-stained immunohistochemically. If discrepancies arose, agreement was reached by consensus.

DNA was extracted from paraffin-embedded tumour tissues, and next-generation sequencing was performed using a panel containing 42 human tumour genes (Table S4), including the following susceptibility genes of PPGL that were designed using Target Capture Probe Design & Ordering Tool from IDT (Integrated DNA Technologies, Inc., USA): CSDE1, EGLN1, EGLN2, EPAS1, FH, HRAS, IDH1, MAX, MDH2, NF1, FGFR1, RET, SDHA, SDHAF2, SDHB, SDHC, SDHD, TMEM127, and VHL. Mutation sites were compared with gene databases (the human reference genome [hg19]), and bioinformatic analyses were performed to determine whether the mutations were pathogenic. Mutations in EGLN1, EGLN2, EPAS1, FH, IDH1, SDHA, SDHAF2, SDHB, SDHC, SDHD, MDH2, and VHL were classified as Cluster 1 based on their association with pseudo-hypoxia pathways. Mutations in FGFR1, HRAS, MAX, NF1, RET, and TMEM127 were classified as Cluster 2 based on their association with kinase signalling pathways. Mutation in CSDE1 was classified as Cluster 3 (Wnt-altered). MAML3 fusion was not studied due to the technical limitation of next-generation sequencing panel.

### Computed tomography image acquisition and analysis

Patients underwent CT scans within a month before surgery, and all CT scans were performed with one of the three scanners: a 16-multi-detector CT (MDCT) (Brilliance 16, Philips), a 64-MDCT (SOMATOM Definition, Siemens), and a 320-MDCT (Aquilion ONE, Toshiba Medical Systems). CT images retrieved from the Picture Archiving and Communication System (Carestream, Canada) were reconstructed with an axial thickness of 1 mm. Two radiologists (H. L. and C. C., with 5 and 25 years of experience, respectively) independently analysed the cross-sectional CT images at the L3 level for body composition parameters including skeletal muscle area, visceral fat area, and subcutaneous fat area using National Institutes of Health ImageJ software (a public domain, Java-based image processing program). Disagreements were resolved in a panel format with one additional researcher (X. Y. or Y. F.). The skeletal muscle index (SMI), visceral fat index (VFI), and subcutaneous fat index (SFI) were calculated by dividing the body composition area by the squared height. Sarcopenia was defined as SMI < 52.4 cm²/m² for males or SMI < 38.5 cm²/m² for females, and visceral obesity was defined as VFI > 100 cm²/m² for both males and females. Representative body composition measurements at the L3 level for patients with normal body composition parameters and patients with parameters consistent with sarcopenia and visceral obesity are presented in Figure 2.

### Statistical analysis

All data were analysed using SPSS Statistics, Version 25.0 (IBM Corp, Armonk, NY, USA). A Shapiro–Wilk test was used to test the data distribution. Continuous normally distributed data were presented as mean (standard deviation) and tested by Student’s t-test, and continuous non-normally distributed data 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. The missing data were filled in using regression estimation. The ROC curve was used to determine the cut-off values for continuous variables at the largest Youden index (Youden index = [sensitivity + specificity] – 1). Variables with $P < 0.05$ in univariate analysis and confounders (age/use of alpha-adrenergic blockade) were considered candidates for multivariate logistic regression analysis. Forward stepwise variable selection was performed to obtain the risk factors, and the results were expressed as odds ratios (ORs) with 95% confidence intervals (CIs). Pearson correlation was used to analyse the correlation between body composition and haemodynamic parameters. All statistical analyses were performed with a two-sided test, and $P < 0.05$ was considered statistically significant.

### Results

#### Patient characteristics

A total of 402 consecutive patients with PPGL were identified for the study period, and 221 patients were included in the final study cohort (Figure 1). The median age of patients at diagnosis was 47 years, 52.0% were males, and 81.4% had PCC (Table 1). The median tumour size was 4.5 cm (range: 1.1 to 17.3 cm), and 78.7% received alpha-adrenergic blockade with prazosin.

Most tumours (71.0%) were tested for positive gene mutations; 21.3% had Cluster 1 mutations, and 49.8% had Cluster 2 mutations (Table 2). Among 221 patients, 99 (44.8%) had sarcopenia, 46 (20.8%) had visceral obesity, and 117 (52.9%) developed intraoperative HDI (Table 1).

All patients in this study were classified as having HDI ($n = 117$) or HDS ($n = 104$). Patients with HDI had larger tumours (4.8 vs. 4.1 cm, $P = 0.001$) and higher urinary outputs of VMA (69.5 vs. 55.0 mg/day, $P = 0.007$) (Table 1). Sarcopenia and visceral obesity were less common in HDI patients (35.9% vs. 54.8%, $P = 0.005$ and 15.4% vs. 26.9%, $P = 0.035$, respectively). However, Cluster 2 mutations were much

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**Note:** This text is a summary of a scientific article, focusing on key points and methods. For detailed reading, the full article should be referred to.
more common in HDI patients (59.8% vs. 38.5%, \( P = 0.002 \)) (Table 2).

As expected, maximal, minimal, and fluctuating values for SBP and DBP in HDI patients were higher (\( P < 0.05 \)) than those in HDS patients (Table 1). Patients with HDI also had higher pulse pressure and higher maximum HR than patients with HDS (all \( P < 0.001 \)). Patients with HDI received more colloidal fluids (\( P = 0.003 \)) and blood products (\( P = 0.005 \)) intraoperatively than patients with HDS. During post-operative recovery, patients with HDI had higher ICU admission rates (37.6% vs. 22.1%, \( P = 0.012 \)) and longer post-operative hospital stays (7 vs. 6 days, \( P = 0.024 \)) than patients with HDS. As for post-operative complications, patients with HDI had higher severe complications (Dindo–Clavien Grades II–V, 31.6% vs. 18.3%, \( P = 0.023 \)). Age, gender, tumour type, BMI, SMI, VFI, SFI, comorbidities, use of alpha-adrenergic blockade or beta-adrenergic blockades, or antihypertensive drugs, pre-anaesthesia blood pressure, pre-anaesthesia HR, surgical approaches, and estimated blood loss were not significantly different between the patients with HDI and those with HDS.

Compared with the patients without sarcopenia, the sub-cohort of patients with sarcopenia had more male (72.7% vs. 35.2%, \( P < 0.001 \)), lower BMI (20.6 vs. 22.8 kg/m\(^2\), \( P < 0.001 \)), higher rates of hypertension (87.9% vs. 72.1%, \( P = 0.004 \)), and a lower incidence of intraoperative HDI (42.4% vs. 61.5%, \( P = 0.005 \)) (Table S2).

**Univariate, multivariate, and correlation analyses**

With univariate and multivariate analyses, several risk factors were identified for intraoperative HDI (Table 3). From the univariate analysis, urine VMA (OR = 1.867, 95% CI = 1.092–3.191, \( P = 0.022 \)), tumour size (OR = 2.472, 95% CI = 1.408–4.339, \( P = 0.002 \)), sarcopenia (OR = 0.462, 95% CI = 0.269–0.793, \( P = 0.005 \)), and Cluster 2 mutations (OR = 2.250, 95%
Table 1 Patient characteristics

| Characteristic                        | Total (N = 221) | HDI (N = 117) | HDS (N = 104) | P-value |
|---------------------------------------|-----------------|---------------|---------------|---------|
| Age (years), median (IQR)            | 47 (38–56)      | 48 (41–56)    | 47 (34–56)    | 0.262   |
| Male, n (%)                          | 115 (52.0%)     | 58 (49.6%)    | 57 (54.8%)    | 0.437   |
| Tumour type (PCC), n (%)             | 180 (81.4%)     | 90 (76.9%)    | 90 (86.5%)    | 0.066   |
| Tumour size (cm), median (IQR)       | 4.5 (3.5–6.2)   | 4.8 (4.0–6.7) | 4.1 (3.3–5.5) | 0.001   |
| BMI (kg/m²), mean (SD)               | 21.9 (3.1)      | 22.0 (3.3)    | 21.7 (3.0)    | 0.467   |

Comorbidities, n (%)

- Hypertension: 175 (79.2%)
- Diabetes mellitus: 28 (12.7%)
- Coronary artery disease: 8 (3.6%)
- Stroke: 10 (4.5%)

Incidentaloma, n (%): 42 (19.0%)

Urinary VMA (μmol/day), median (IQR) 60.7 (36.5–104.9)

 Alpha-adrenergic blockades (prazosin)

- Usage, n (%): 174 (78.7%)
- Maximum dose (mg/day), median (IQR): 6 (4–12)
- Cumulative dose (mg): 44.0 (14.6–89.5)
- Duration of usage (days), median (IQR): 6.0 (1.0–11.0)
- Use of beta-adrenergic blockades, n (%): 43 (19.5%)
- Use of antihypertensive drugs, n (%): Calcium channel blockades 18 (8.1%), Others 7 (3.2%)

Pre-anaesthetic blood pressure (mmHg), median (IQR)

- SBP: 135 (120–156)
- DBP: 80 (71–90)
- Pre-anaesthetic HR (b.p.m.), median (IQR): 80 (72–90)

Surgical approaches, n (%)

- Laparoscopic surgery: 155 (70.1%)
- Open surgery: 67 (29.6%)

Estimated blood loss (mL), median (IQR) 100 (50–300)

Intraoperative intake, n (%)

- Crystal fluids > 1000 mL: 139 (62.9%)
- Colloidal fluids > 1000 mL: 78 (35.3%)
- Blood products: 67 (30.3%)

Haemodynamic variables (mmHg), median (IQR)

- Maximum SBP: 180 (160–200)
- Minimum SBP: 100 (90–110)
- ASBP: 76 (51–102)
- Maximum DBP: 100 (90–110)
- Minimum DBP: 60 (53–70)
- ΔSBP: 40 (27–58)
- MAP: 73 (66–83)
- PP: 79 (60–93)

Intraoperative HR (b.p.m.), median (IQR)

- Maximum HR: 100 (89–119)
- Minimum HR: 70 (62–80)

Haemodynamic instability, n (%)

- SBP > 160 mmHg and (or) MAP < 60 mmHg: 154 (69.7%)
- SBP > 180 mmHg and (or) MAP < 60 mmHg: 117 (52.9%)

Length of surgery (min), median (IQR) 135 (101–185)

Post-operative recovery

- ICU admission, n (%): 67 (30.3%)
- PHS (days), median (IQR): 7 (5–8)

Post-operative complications, n (%)

- Mild (none and Grade I): 165 (74.7%)
- Severe (Grades II–V): 56 (25.3%)

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; HDI, haemodynamic instability; HDS, haemodynamic stability; HR, heart rate; ICU, intensive care unit; IQR, interquartile range; MAP, mean arterial pressure; PCC, pheochromocytoma; PHS, post-operative hospital stays; PP, pulse pressure; SBP, systolic blood pressure; SD, standard deviation; VMA, vanillylmandelic acid; ΔDBP, maximum DBP–minimum DBP; ΔSBP, maximum SBP–minimum SBP.

*VMA reference range: 10.0–30.0 μmol/day.

Data of six patients were outliers.

According to Dindo–Clavien classification.
Gene mutations, \( n \) (%)

| Gene mutations, \( n \) (%) | Total (\( N = 221 \)) | HDI (\( N = 117 \)) | HDS (\( N = 104 \)) | \( P \)-value |
|-----------------------------|------------------------|---------------------|---------------------|-------------|
| Negative                    | 64 (29.0%)             | 28 (23.9%)          | 36 (34.6%)          | 0.006       |
| Cluster 1 mutations         | 47 (21.3%)             | 19 (16.2%)          | 28 (26.9%)          |             |
| Cluster 2 mutations         | 110 (49.8%)            | 70 (59.8%)          | 40 (38.5%)          |             |

Body composition index (\( \text{cm}^2/\text{m}^2 \))

| Variables                  | Total (\( N = 221 \)) | HDI (\( N = 117 \)) | HDS (\( N = 104 \)) |
|----------------------------|------------------------|---------------------|---------------------|
| SMI                        | 46.2 (40.5–51.9)       | 46.4 (42.5–53.1)    | 45.5 (38.6–51.6)    |
| VFI                        | 23.2 (11.3–36.6)       | 21.1 (10.7–33.7)    | 25.8 (12.2–38.5)    |
| SFI                        | 37.0 (21.6–57.0)       | 36.3 (22.2–56.8)    | 37.2 (21.1–57.1)    |

Body composition, \( n \) (%)

| Variables                  | Total (\( N = 221 \)) | HDI (\( N = 117 \)) | HDS (\( N = 104 \)) |
|----------------------------|------------------------|---------------------|---------------------|
| Sarcopenia                 | 99 (44.8%)             | 42 (35.9%)          | 57 (54.8%)          |
| Visceral obesity           | 46 (20.8%)             | 18 (15.4%)          | 28 (26.9%)          |

Note: Data were presented as median (interquartile range).

Abbreviations: HDI, haemodynamic instability; HDS, haemodynamic stability; SFI, subcutaneous fat index; SMI, skeletal muscle index; VFI, visceral fat index.

\( ^a \)No mutation in CSDE1, which is associated with Wnt-altered subtype, was detected in this cohort of 221 patients.

Cl = 1.200–4.218, \( P = 0.011 \) were candidate risk factors for multivariate analysis. After adjusting for age and use of alpha-adrenergic blockade, multivariate analysis showed that urine VMA \( \geq 58 \) \( \mu \text{mol/day} \), tumour size \( \geq 4 \) cm, and Cluster 2 mutations were significant independent risk factors for HDI. The risk of intraoperative HDI in patients with a urine VMA \( \geq 58 \) \( \mu \text{mol/day} \) was higher than that for patients with urine VMA \( < 58 \) \( \mu \text{mol/day} \) (adjusted OR = 1.840, 95% CI = 1.012–3.347, \( P = 0.046 \)). Patients with a tumour size \( \geq 4 \) cm had a 2.278-fold higher risk of intraoperative HDI than those with tumours \( < 4 \) cm (95% CI = 1.242–4.180, \( P = 0.008 \)), and patients with Cluster 2 mutations had a 2.199-fold higher risk of intraoperative HDI than those with negative mutations (95% CI = 1.128–4.285, \( P = 0.021 \)).

Multivariate analysis showed that sarcopenia was an independent protective factor for HDI in patients with PPGL. The risk of intraoperative HDI in patients with sarcopenia was 0.475-fold lower than that in patients without sarcopenia (95% CI = 0.266–0.846, \( P = 0.012 \)).

Pearson correlation analysis of 221 patients with PPGL showed that SMI was positively correlated with maximum SBP (male: \( r_m = 0.208, P_m = 0.026 \)), while VFI was positively correlated with MAP (\( r = 0.163, P = 0.015 \)) (Figure S2). However, there was no correlation between SMI and MAP, between SMI and \( \Delta \)SBP, between VFI and maximum SBP, or between VFI and \( \Delta \)SBP (all \( P > 0.05 \)).

Subgroup analysis

Subgroup analysis showed that the mean tumour size of PGL patients with Cluster 2 mutations was larger than that of patients with Cluster 1 mutations (6.7 vs. 3.7 cm, \( P = 0.014 \)) (Table S3). Males with Cluster 2 mutations had a higher SMI than males with Cluster 1 mutations (53.1 ± 7.7 vs. 45.7 ± 8.7 cm\(^2\)/m\(^2\)), but no such difference was observed in females with PPGL. Similarly, sarcopenia with Cluster 2 mutations was less common than sarcopenia with Cluster 1 mutations in males.

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### Table 2: Body composition parameters and gene mutations in patients with pheochromocytoma or paraganglioma

| Variables                  | Total (\( N = 221 \)) | HDI (\( N = 117 \)) | HDS (\( N = 104 \)) | \( P \)-value |
|----------------------------|------------------------|---------------------|---------------------|-------------|
| Negative \( n \) (%)       |                        |                     |                     |             |
| Cluster 1 mutations        |                        |                     |                     |             |
| Cluster 2 mutations        |                        |                     |                     |             |
| Body composition index     |                        |                     |                     |             |
| SMI                        | 46.2 (40.5–51.9)       | 46.4 (42.5–53.1)    | 45.5 (38.6–51.6)    |
| VFI                        | 23.2 (11.3–36.6)       | 21.1 (10.7–33.7)    | 25.8 (12.2–38.5)    |
| SFI                        | 37.0 (21.6–57.0)       | 36.3 (22.2–56.8)    | 37.2 (21.1–57.1)    |
| Body composition, \( n \) (%) | 99 (44.8%)             | 42 (35.9%)          | 57 (54.8%)          |

Abbreviations: CI, confidence interval; OR, odds ratio; VMA, vanillylmandelic acid.

\( ^a \)Adjusted by age and use of alpha-adrenergic blockade.
(55.2% vs. 84.0%, \( P = 0.012 \)). In contrast, there were no significant differences in VFI and visceral obesity between patients with Cluster 1 and Cluster 2 mutations, either for males or for females. There were also no significant differences in urine VMA between patients with Cluster 1 and Cluster 2 mutations.

### Discussion

This study showed that urine VMA, tumour size, body composition, and gene mutations were associated with intraoperative haemodynamics. Specifically, patients with urine VMA \( \geq 58 \mu\text{mol/day} \), tumour size \( \geq 4 \text{ cm} \), and Cluster 2 mutations had an increased risk of HDI during surgery for PPGL, while patients with sarcopenia had a decreased risk. To our knowledge, this was the first study to assess the potential impact of body composition and genotype on intraoperative haemodynamics in patients with PPGL.

Our finding of Cluster 2 mutations being an independent risk factor for HDI in patients with PPGL was in general agreement with the literature on various genetic mutations leading to different catecholamines secretion. Tumours with Cluster 2 mutations express phenylethanolamine-N-methyltransferase, thereby produce epinephrine, and are characterized by larger tissue stores of catecholamines than tumours with Cluster 1 mutations that do not produce appreciable amounts of epinephrine. Although tumours with Cluster 2 mutations do not secrete catecholamines in the same high continuous manner as tumours with Cluster 1 mutations, they can be more easily provoked to secrete catecholamines and are generally considered to have more episodic secretion than tumours with Cluster 1 mutations. Therefore, it should not be surprising to find Cluster 2 mutations being a risk factor for HDI.

As we have more recently shown, the influence of genotype on the catecholamine phenotype in PPGLs extends from germline to somatic mutations and from Western to Chinese populations. Epinephrine produced by Cluster 2 tumours strongly activates cardiac beta-adrenergic receptors to increase myocardial contractility, HR, and cardiac output, resulting in significant increases in SBP. On the other hand, noradrenaline produced by tumour with Cluster 1 mutations principally acts on peripheral vascular alpha-adrenergic receptors, causing an increase in DBP. In our study, patients with intraoperative HDI had a higher SBP and a greater pulse pressure than patients with HDS. Therefore, we speculate that the epinephrine-producing adrenergic phenotype of tumours due to Cluster 2 mutations may contribute to intraoperative HDI in patients with these tumours. This might reflect not only differences in actions of epinephrine and norepinephrine but also the episodic nature of catecholamine secretion in tumours with Cluster 2 mutations.

Our hypothesis for potential mechanisms links tumour size, Cluster 2 mutations, sarcopenia, and visceral obesity to haemodynamics during surgery for PPGL. We hypothesized that patients with Cluster 2 mutations and/or larger tumours may secrete episodically higher concentrations of catecholamines with a greater proportion of epinephrine as compared with the patients without Cluster 2 mutations and/or with smaller tumours. This, in turn, may increase myocardial contraction and SBP. Independent support for this concept is provided by another study that has linked epinephrine-producing tumours with more severe cardiac changes than PPGLs that produce only norepinephrine. Also in line with other observations, higher concentrations of catecholamines may alter body composition through their effects on metabolism of skeletal muscle and visceral fat.

There are several possible explanations for why sarcopenia or visceral obesity might negatively affect haemodynamics. Sarcopenia promotes the senescence of vascular smooth muscle cells and endothelial cells through the renin-angiotensin system, leading to vascular dysfunction. Visceral fat was shown to be independently associated with concentric left ventricular remodelling and adverse haemodynamics. We speculate that the blunted blood pressure response in patients with sarcopenia might be associated with diminished myocardial contractility and vascular dysfunction. Our study cohort, in which about half of patients had sarcopenia, was consistent with prior research, indicating that patients with PCC have reduced skeletal muscle mass. Therefore, these patients may not be as able to respond to haemodynamic fluctuations as patients without sarcopenia or visceral obesity. However, the literature is limited and much remains unclear. These speculations need further mechanistic studies such as tissue biopsy for detailed examination of muscle and fat to assess the underlying pathophysiology of sarcopenia and HDI in patients with PPGL.

In the present study, we found that SMI was positively correlated with maximal SBP and change in SBP, while VFI was positively correlated with MAP. These results were generally in line with prior research indicating that abdominal visceral obesity may predict blunted changes in SBP and MAP. Prior research found that visceral fat area was negatively correlated with left ventricular ejection fraction, thus affecting SBP. We speculated that patients with sarcopenia and visceral obesity may have vascular and cardiac dysfunction due to abnormal body composition, which may lead to blunted haemodynamic responses during surgery.

We found potential associations among the contributing factors to intraoperative HDI: urine VMA, tumour size, body composition, and genotype (Table S2). For example, the patients with PGL and Cluster 2 mutations had larger tumours. Small PGL tumours should be typically asymptomatic because they are expected to release low amounts of catecholamines and tend to localize to the retroperitoneum with no tumour compression symptoms. Therefore, PGL tumours were usu-
ally large upon diagnosis as in our study, and the catechol-
amines stored within the tumours may be released into the
blood during surgery, resulting in HDI. Additionally, we found
it less common to have patients with both sarcopenia and
Cluster 2 mutations. We speculate that patients with Cluster
2 mutations may be less prone to muscle atrophy and fat re-
distribution than those without these mutations.35,38

Prior research has revealed risk factors for intraoperative
HDI in patients with PPGL, including age ≥ 50 years, preoper-
ative blood pressure ≥ 130/80 mmHg,6 preoperative SBP
fluctuation > 50 mmHg,7 five-fold increase in urine epinephrine,4
diabetes/prediabetes7,8 larger tumour size, and retroperitoneal
adrenalectomy.9,12,39 We incorporated all these known risk factors from literature into our study,
and the only consistent result was that tumour size ≥ 4 cm
was a risk factor for intraoperative HDI.9 The other reported
risk factors were not associated with intraoperative HDI in
our study. We speculate that the differences in the risk factor
assessments may be partly due to the differences in study co-
horts. Nevertheless, we found that Cluster 2 mutations were
a new risk factor for intraoperative HDI, indicating the
relevance of genetic mutations in haemodynamic responses
associated with PPGL during surgery.

It was intriguing to observe the finding of sarcopenic
patients having higher rates of hypertension but lower
incidence of intraoperative HDI. Previous published studies
have indicated the association between sarcopenia and
hypertension.40,41 Literature has also implicated that hyper-
tension may not predispose patients to have intraoperative
HDI.42 We speculate that patients with sarcopenia may have
adapted to the long-term effects of high blood pressure, and
their haemodynamics may not fluctuate dramatically in re-
sponse to anaesthesia, surgery, and other stimulations during
surgery. In addition, there may be other factors related to hy-
pertension and haemodynamics, including age, sarcopenia,
and catecholamine, which is need of further study to under-
stand the mechanism underlying HDI.

It should be pointed out that we assessed body composi-
tion parameters using non-invasive preoperative CT images,
which were routinely acquired as part of standard clinical
care. No additional imaging was needed. Our study should
motivate further research into the mechanisms of intraopera-
tive HDI and the potential clinical use of body composition
analysis in the preoperative evaluation of patients with PPGL.

There were several limitations to this study. First, this was
a retrospective single-centre study, so that missing data, con-
founders, and selection bias could not be avoided. Neverthe-
less, we maximized the study cohort, adjusted confounders,
and used stratification, and subgroup analysis to minimize
the effects of various confounding variables. Second, the inci-
dence of HDI in this study was higher than that in previous
studies, possibly due to differing definitions of HDI, potential
case selection bias, and ethnic differences between Chinese
and Western populations. Third, plasma concentrations or
urinary outputs of catecholamines and metanephrines were
not available at our hospital over the time course of the
study. Only urine VMA was consistently available. Conse-
quently, we were unable to explore the relevance of the gene
clusters, concentrations of catecholamines, and HDI, which
would have produced more meaningful data in our search
of risk factors for HDI. Finally, CT scans were obtained using
three different CT scanners. There might be differences in
scanning parameters among the scanners, which could have
affected the CT tissue density values and contributed to sub-
tle variations in body composition measurements.

In summary, we identified several risk factors associated
with intraoperative HDI in patients with PPGL. Specifically,
we found that urine VMA, tumour size ≥ 4 cm, and Cluster
2 mutations were independent risk factors for intraoperative
HDI, while sarcopenia was associated with stable haemody-
namics with blunted responses to blood pressure change.
Our findings indicate that inclusion of body composition
and genotype in the overall assessment of patients with PPGL
should help to prevent perioperative haemodynamic

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Online supplementary material

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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