

## Peer Review File

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### Reviewer A

#1. The title is not accurate and did not indicate the clinical research design of this study, i.e., a diagnostic test. The term “important” is very vague.

A) We agree and removed the term ‘important’ from Title

Accordingly, we changed the title as follows as you and another reviewer:

“Mass Size Is a Major Predictor of Hypertensive Attack during Surgery in Patients with Paraganglioma of Retroperitoneum.”

#2. Second, the abstract needs further revisions. In the background, the authors did not explain the clinical needs and clinical significance of the focus on blood pressure fluctuation and what has been unknown on the predictive ability of mass size for blood pressure fluctuation. The objectives here are also not consistent with the title, i.e., the predictive ability of mass size for blood pressure fluctuation, not factors related to surgical complications such as fluctuation of blood pressure. In the methods, please describe the inclusion of subjects, the assessment of blood pressure, and measurement of mass size. In the results, please also report the 95% CIs of AUC, sensitivity, and specificity. Given the small sample size and the AUC lower than 0.8, the conclusion should be made with cautions.

A) We revised Abstract and Methods sections as your recommendation.

“Surgical manipulation of paraganglioma can induce a massive release of catecholamines leading to fluctuation of blood pressure (FBP). But it has been not known about risk factors to cause FBP because paragangliomas of urinary bladder and retroperitoneum are notably rare tumors and have been recorded as case report or series. We investigated the relationship between mass size among various factors and FBP during surgery in patients with paraganglioma.” in the Background of Abstract.

“We analyzed the risk factors such as age, sex, height, weight, blood pressure before surgery, history of hypertension, pre-operative symptoms, mass location, and mass size impacting FBP in 24 patients with retroperitoneal paragangliomas including urinary bladder among them. FBP

was defined as systolic blood pressure > 180 mmHg during excision of the mass from the electric medical chart. The predictive power was assessed by the area under the curve of the receiver operating characteristic curve.” in the Methods of Abstract and in the Methods section of main body.

95% CI of AUC was 0.635 – 0.981 and we revised Methods of Abstract and Results section of main body. Usually, AUC > 0.7 or 0.75 shows a relatively good prediction rate. As your opinion, conclusion may be made with cautions, however, there was a significant difference in terms of mass size between groups with (n=11) and without (n=13) fluctuation of blood pressure during surgery (p=0.007).

And as another reviewer’s recommendation and to avoid confusion of definition, we changed the term “fluctuation of blood pressure” or “FEP” into “hypertensive attack” in all manuscript.

#3. Third, the introduction of the main text is poor. The authors should review the clinical significance and needs for the research focus of blood pressure fluctuation during the surgical treatment, factors associated with blood pressure fluctuation, and what the knowledge gap is in relation to the mass size. The objectives should be further clarified, i.e., associated factors, or the diagnostic accuracy of mass size for blood pressure fluctuation. BTW, the definition of blood pressure fluctuation should be provided.

Thank you for your nice comment. We planned to introduce explanation of paraganglioma in the Introduction section. As your recommendation, we added the clinical significance and research into Introduction section as following:

“Thus, preoperative medication of combined  $\alpha$ - and  $\beta$ -adrenergic blocker therapy is necessary to control and prevent intraoperative hypertension. Especially, predicting which patients may have intraoperative instability of blood pressure or hypertension would be useful because it may facilitate selection of a drug regimen wherein patients predicted more likely to have hemodynamic instability during surgery.<sup>11,12</sup> Previous studies have found a level of catecholamine as a predictor of hemodynamic instability in pheochromocytoma.<sup>13,14</sup> But unlike pheochromocytoma, it is difficult to diagnose paraganglioma before surgery as already mentioned, so it is not easy to test for catecholamine and pretreat medication before surgery. Therefore it is needed that other factors that can predict hypertensive attack or hemodynamic instability before surgery.”

#4. Fourth, in the methodology of the main text, the clinical research design should be clearly defined, i.e., diagnostic test or case-control study for risk factors. The authors must provide their considerations for such a small sample size, which is not adequate for investigating the diagnostic accuracy and risk factors. Please describe the assessments of blood pressure and mass size. The definition of blood pressure fluctuation is problematic, because in general, blood pressure fluctuation is the variability in the DBP and SBP. The authors in fact, defined a very high SBP. In statistics, please ensure  $P < 0.05$  is two-sided. Please describe the determination of the cut-off value of mass size and the calculation of sensitivity and specificity. Threshold values of AUC, sensitivity and specificity for a good diagnostic test should also be reported.

A)

1) Research design

Yes, we agree. We revised Methods section as your recommendations:

“We analyzed the risk factors impacting ~~surgical complications such as massive bleeding or~~ fluctuation of blood pressure in 24 patients with retroperitoneal paragangliomas including 5 UB paragangliomas.”

“The risk factors such as age, sex, height, weight, blood pressure before surgery (systolic and diastolic), history of hypertension, pre-operative symptoms, mass location (bladder vs. retroperitoneum) and mass size were compared between groups with (n=11) and without (n=13) hypertensive attack ~~fluctuation of blood pressure~~ during surgery.” was added into Methods section.

2) Small sample size and diagnostic accuracy

Yes. We agree. We already mentioned that as study limitation in the Discussion section. But, paragangliomas are extremely rare and this is a first report to reveal the relationship of mass size and hypertensive attack in pure paraganglioma patients. As base of current results and paper, we further have a plan to investigate that with national data.

3) Definition of blood pressure is problematic.

Yes, we also originally thought so. During surgery of pheochromocytoma, systolic and diastolic arterial blood pressure and heart rate values were automatically checked in anesthesiology department, continuously, and digitally recorded by invasive measurement through an arterial line in the radial artery. Central venous pressure was monitored in all patients. Usually, systolic arterial pressure (SAP)  $> 160$  mmHg was treated with intravenous boluses of nicardipine 2–4 mg to maintain SAP between 120 and 160 mmHg. Intravenous boluses of esmolol 1–1.5 mg/kg

were used if the heart rate exceeded 100 beats/min. In reference of Kwon SY et al. ICUrology 2016, hypertensive attack was defined as a systolic blood pressure >180 mmHg at any time during surgery. Usually the term “hypertensive attack” is similarly used in this kind of study as the term, “hemodynamic instability” and “fluctuation of blood pressure”. In most case, paragangliomas produce catecholamines such as epinephrine, norepinephrine, metanephrine and dopamine. Thus, they can induce severe hypertension, tachycardia and even death rather than hypotension. Therefore we made definition of fluctuation of blood pressure as a systolic blood pressure >180 mmHg at any time during surgery.

As your and another reviewer’s recommendations and to avoid confusion of definition, we changed the term “fluctuation of blood pressure” or “FEP” into “hypertensive attack” in all manuscript.

#### 4) Statistical issues

We already mentioned “All statistical analyses were two-sided, and  $p < 0.05$  was considered statistically significant.” in Methods section. And mention about ROC curve and AUC was also revised as a previous your comments.

#### **Reviewer B**

#1. The topic is out of sink with the contents of the paper. The topic limits the authors to study the effects of mass on blood pressure fluctuations in surgery yet authors have other objectives of looking for risk factors blood. No chart of mass measurements versus blood pressure.

Sorry. From another reviewer’s recommendation, we made revision about your comments as following:

“We investigated the relationship between mass size and hypertensive attack during surgery in patients with paraganglioma.”

And we added mass measurements and blood pressure into Methods section as following:

“Hypertension was defined as a systolic blood pressure >140 mmHg or a diastolic blood pressure >90 mmHg.”

“The size of the paraganglimoma was obtained in three dimensions of CT scan, and longest length among them was determined as the size of the mass.”

#2. It’s difficult to compare blood pressure fluctuations when you have more than one surgical

approach.

The pre- morbid conditions of these patients have an effect on blood pressure during surgery.

This is not captured.

Blood losses plotted against tumor size are not captured.

Yes, we agree. The patients included in current study is heterogeneous. Surgical approach is various. In bladder transurethral mass resection was used in three patients. But the patients with small mass of current study did not have fluctuation of blood pressure during surgery. In references (#18 and #19), at TURBT initiation, patients' systolic blood pressure was acutely elevated to over 180 mmHg. ) Li et al. (BMC Anesthesiol 2020;20:147) revealed type of surgery (transurethral vs. open vs. lapa) had a significant difference in developing postoperative complications during pheochromocytoma and paraganglioma surgery. But, there was no evidence about surgical type and hypertensive attack during pheochromocytoma surgery. In a previous study, DM was significantly related to hemodynamic instability, however, most of studies had no significant relation in terms of pre-operative obesity, DM, hypertension, etc. to hemodynamic instability. In our results, there were 4 patients with needs of transfusion and all 4 patients also had hypertensive attack. As your recommendation, it would be interesting to reveal relation of exact estimated blood loss and tumor size with more patients.

As it was previously mentioned as study limitations, the number of patients in current study was small because paraganglioma is notably rare. Maybe multicenter studies are required for more accurate results to cover your comments. As base of current results and manuscript, we further have a plan to investigate that with national data.

Thank you.

#3. Tumor were located in different areas, which impacts blood pressure differently.

Yes, we agree with you. Therefore just retroperitoneum and bladder paragangliomas were included in the current study. Of course, among the retroperitoneum, tumors were also located in different areas. But, tumor was so rare, we could not sort according to the specific areas in retroperitoneal area. We removed 8 among 32 paragangliomas in current study for your reason. If the study will carry with national data, we will be able to define that.

#4. No mention on which tumors were silent and which were not. Some paragangliomas

produce catecholamines while others do not. Use of alpha adrenergic antagonists are not documented to those patients with secretory tumours.

It is a good point. We already mentioned that “But unlike pheochromocytoma, it is difficult to diagnose paraganglioma before surgery as already mentioned, so it is not easy to test for catecholamine and pretreat medication before surgery. Therefore it is needed that other factors that can predict hypertensive attack or hemodynamic instability before surgery.”

Unlike of pheochromocytoma, we could not perform the catecholamine test before surgery in paraganglioma because of difficulty in diagnosing before surgery. Therefore we could evaluate that tumors were silent or were not.

In study, just 7 (29.2%) among 24 patients had a hormonal tests including catecholamine before surgery and it was reported with a similar incidence in previous studies. All patients with pre-operative diagnosis of paraganglioma used alpha adrenergic blocker irrespective of hormonal abnormality of secretory tumor.

### Reviewer C

This article focus on a potential life-threatening complication during the surgical removal of paraganglioma, which remains a challenge for all practitioners, especially since this tumor is rare.

However, many points need to be clarified and corrected.

1- The definition of “Fluctuation of blood pressure” is not correct since it not describes a variation of blood pressure but only an acute systolic blood pressure elevation  $> 180$  mmHg. It would be more accurate to define it as "a severe elevation in systolic blood pressure", and change this term throughout the manuscript (Eur Heart J Cardiovasc Pharmacother. 2019 Jan 1;5(1):37-46. doi: 10.1093/ehjcvp/pvy032). Usually, intraoperative hemodynamic instability is defined by hypertension, hypotension or abnormal tachycardia.

A) Yes. I know. Therefore, before submission, we decided on the term “fluctuation of blood pressure” after taking much consideration. In reference of Kwon SY et al. ICUrology 2016, hypertensive attack was defined as a systolic blood pressure $>180$  mmHg at any time during surgery. Usually the term “hypertensive attack or intraoperative hypertension” is similarly used

in this kind of study as the term, “hemodynamic instability” and “fluctuation of blood pressure”. In most case, paragangliomas produce catecholamines such as epinephrine, norepinephrine, metanephrine and dopamine. Thus, they can induce severe hypertension, tachycardia and even death rather than hypotension. Therefore we made definition of fluctuation of blood pressure as a systolic blood pressure >180 mmHg at any time during surgery.

In your recommendation, to avoid confusion of definition, we changed the term from “fluctuation of blood pressure” into “hypertensive attack”.

2- What the authors define as “preoperative hypertension” is not explicit: is it the presence of hypertension before the diagnosis of paraganglioma or only patients receiving anti-hypertensive therapy before surgery? In addition, the number of patient treated before the operation or the type of drug treatment (alpha-blocker/ beta-blockers...) are not specified. It is very important to clearly define this point, because it is well known to be major in the perioperative management of pheochromocytoma and paraganglioma. One of the elements that the authors could specify would be the number/percentage of patient with adequate blood pressure before the surgery (e.i < 130/85mmHg) instead of the mean values of systolic and diastolic blood pressure.

A) Yes. You are right. There was no pre-operative hypertension in the current Manuscript. Because of History of hypertension (n=11, 45.8%), we added to the Methods section as “Hypertension was defined as a systolic blood pressure >140 mmHg or a diastolic blood pressure >90 mmHg.” As we previously mentioned, diagnosis of paraganglioma from imaging study is very difficult. Therefore, relationship of incidental finding of mass from CT scan and hypertension is so hard to assume. The patients with preoperative hypertension had routine anti-hypertensive drugs such as calcium channel block or ACE inhibitor or alpha blocker, etc. and control of hypertension. As already mentioned in Methods section, The mean systolic and diastolic blood pressure were  $128.1 \pm 15.4$  mmHg and  $76.8 \pm 8.6$  mmHg, respectively (Table 1).

As your recommendation, we added following sentence into Method section:

“The patients with preoperative hypertension had routine anti-hypertensive drugs such as calcium channel block or ACE inhibitor or alpha blocker, etc. and control of hypertension.” and “There were five patient with systolic blood pressure > 140 mmHg or diastolic blood

pressure > 90 mmHg, however, none of these patients had hypertensive attack or massive bleeding during surgery.”

3- It is not mentioned the type of anesthetic drugs used during the surgery, while some of them are known to have a potential impact on blood pressure. Maybe the authors do not have all the data but that should be noted and discussed as an additional bias.

A) Yes, you are right. Types of anesthetic drugs used during the surgery are known to have a potential impact on blood pressure. But all patients was used same anesthesia drugs and same general anesthesia method in our institution.

Usually during surgery of pheochromocytoma, systolic and diastolic arterial blood pressure and heart rate values were automatically in anesthesiology department, continuously, and digitally recorded by invasive measurement through an arterial line in the radial artery. Central venous pressure was monitored in all patients. Usually, systolic arterial pressure (SAP) > 160 mmHg was treated with intravenous boluses of nicardipine 2–4 mg to maintain SAP between 120 and 160 mmHg. Intravenous boluses of esmolol 1–1.5 mg/kg were used if the heart rate exceeded 100 beats/min.

4- Regarding the methodology, some results are given in the section « method » (patients demography..) or in the discussion (number of patients with pre operative évaluation for catecholamine) . All results must be placed in the results section.

A) Yes we re-arranged that as your recommendation. All results including patients' demography were moved into the Results section.

The description about “pre-operative hormone evaluation (7/24, 29.2%)” in Discussion section was just cited to explain that it is relatively difficult to test hormonal analysis before surgery in paraganglioma compared to pheochromocytoma. And it was already described in the Results section.

5- Table 1. It would be interesting to clarify the modalities of diagnosis : incidentalomas (CT), patients with adrenal-related symptomes, during surgery.

A) Yes, we changed that as your recommendation. Two variables (incidentaloma and adrenal-



related symptoms during surgery) was inserted into the Table 1.

\*adrenal-related symptoms: tachycardia (frequency > 100 bpm), desaturation (SpO<sub>2</sub> < 90%), acidosis (pH < 7.3)

6- English language need to be improve (for exemple « requirement for transfusion of blood » to change to « need for a blood transfusion », « disease specific death » to change to « disease related death » ...)

A) The whole manuscript was already edited with English (native speaker) Proofreading Company (<https://www.enago.co.kr/>). But we had again checked the English correction.

7- Important references related to the subject are missing. For exemple Kim JH. *Frontiers in Endocrinology* 2022 – Kim JH. *scientific reports* 2021 – Uslar T. *J of the Endocrin Society* 2020

A) Yes. We added the above references into references section as references in the Introduction section.

“Especially, predicting which patients may have intraoperative instability of blood pressure would be useful because it may facilitate selection of a drug regimen wherein patients predicted more likely to have hemodynamic instability during surgery.<sup>11,12</sup> Previous studies have found a level of catecholamine as a predictor of hemodynamic instability.<sup>13,14</sup> But unlike pheochromocytoma, it is difficult to diagnose paraganglioma before surgery as already mentioned, so it is not easy to test for catecholamine and pretreat medication before surgery.”

12. Kim JH, Lee HC, Kim SJ, et al. Characteristics of Intraoperative Hemodynamic Instability in Postoperatively Diagnosed Pheochromocytoma and Sympathetic Paraganglioma Patients. *Front Endocrinol (Lausanne)* 2022 Feb 24;13:816833.

13. Ma L, Shen L, Zhang X et al. Predictors of hemodynamic instability in patients with pheochromocytoma and paraganglioma. *Journal of Surgical Oncology* 2020;122:803–8.

14. Kim JH, Lee HC, Kim SJ, et al. Perioperative hemodynamic instability in pheochromocytoma and sympathetic paraganglioma patients. *Sci Rep* 2021 Sep 17;11:18574.

1- Page 3, line 18: number of patients with “fluctuation of blood pressure” is 13

A) No, the number of patients with FBP was 11 and without was 13. “Fluctuation of blood pressure” was replaced to FBP.

2- Page 4 : intraoperative hypertension can be proposed as a keyword. Mistake in the spelling of paraganglioma

A) Thank you. We corrected the simple error of mis-spelling in Key Words. And we inserted “intraoperative hypertension” into Key Words.

1- Page 9, line 15 : « the mean size of the bladder mass was significantly smaller than that of the retroperitoneal mass except for the bladder » is not clear. « except for the bladder » can be removed.

A) Yes. We corrected that. “except for the bladder” was removed from context as your recommendation.

2- Page 12, lines 17-18: « Considering recent developments, robotic surgery may be helpful depending on the operator. This should help reduce fluctuation of blood pressure and severe complications » : please explain and argue your point, or remove this sentence.

A) Li et al. (BMC Anesthesiol 2020;20:147) revealed type of surgery (transurethral vs. open vs. lapa) had a significant difference in developing complications during pheochromocytoma and paraganglioma surgery. But, there was no description about robot surgery.

To avoid confusion or argument, we removed the sentences “Considering recent developments, robotic surgery may be helpful depending on the operator. This should help reduce fluctuation of blood pressure and severe complications.” from the Discussion section as your recommendation.

3- Figure 2 and 3 are not mentioned in the text of the manuscript. Figure 3 does not add relevant information and could therefore be removed.

A) Yes. As your recommendation, we removed figure 3 from current manuscript.

But, figure 2 was mentioned in the Results section as “ROC analysis showed that the AUC for predicting surgical complications according to mass size was 0.808 (Fig. 2). At cutoff mass

size of 4.25 cm, the sensitivity and the specificity were 72.7% and 76.9%, respectively (95% CI 0.635 – 0.981).”

4- Page 13, line 3: reference 14 should be replaced by references 12 and 13.

A) Yes, we corrected that. Thank you.

5- Why is genetic screening not mentioned by the authors when it is recommended for all patients with paraganglioma ? It would have been interesting to know if there was a difference between patients with severe systolic blood elevation during surgery, regarding the presence or absence of genetic mutation. This should be discussed if there is no data.

A) Yes, we also think that genetic results would be interesting. But, we have no data about it.

We added following sentences into Discussion section as your recommendation:

“Pheochromocytoma and paraganglioma are the most heritable tumors and autosomal dominant hereditary cancer diseases.<sup>24</sup> In our country, generally genetic screening is not recommended for patients with paraganglioma although clinical practice guidelines of paraganglioma recommend testing for germline variants in all patients.<sup>25,26</sup> First, gene sequencing is expensive in our country. Second, there was a just single tumor in retroperitoneum and bladder in all patients. Third, there was no signs such as multiple endocrine neoplasia type 2 caused by RET gene, neurofibromatosis type I caused by NF1 gene, and von Hippel-Lindau disease caused by VHL gene in all patients.”

6- Reference 3 is not directly related to the topic.

A) Yes, we corrected that. We changed reference 3 into a reference related to the topic.

Reference 3. Purnell S, Sidana A, Maruf M, et al. Genitourinary paraganglioma: Demographic, pathologic, and clinical characteristics in the surveillance, epidemiology, and end results database (2000-2012). *Urol Oncol* 2017;35:457.e9-14.