Peer Review File

Article information: https://dx.doi.org/10.21037/tp-21-245

Reviewer A

This is an important study regarding the risk of chemotherapy induced vomiting in patients with retinoblastoma. Not much is known about risk for vomiting in this group of patients. However, I do have several major concerns about this study which would need to be addressed prior to acceptance for publication.

PROS:

Comment 1: very large, single institution study which included 803 retinoblastoma patients. This is an enormous number for this type of research, and therefore would be important to publish

Reply 1: Thank you very much for your comments! Due to the large population of China and the centralizing tendency of Department of Ophthalmology of Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine in diagnosis and treatment for orbital diseases and eye neoplasm in China, a single center study with large patient population is practical. After discovering the law in a single center, we hope to verify it in multiple centers in the next step.

Comment 2: heterogenous treatment plans, including a large number of patients who received intraarterial and others who received intravenous chemotherapy

Reply 2: Thank you very much for your comments! Intra-arterial chemotherapy and intravenous chemotherapy are the two most common treatment of RB at present. They have been carried out in our and other large RB diagnosis and treatment centers for years with well-established standard operation process. Many RB diagnosis and treatment centers can only carry out one of the treatments mentioned above, while both of them areimplemented in ours, resulting in no restriction on the choice of schemes.

Comment 3: ~9% of those who only received intraarterial chemotherapy had vomiting which is surprising; 25%

Reply 3: Thank you very much for your comments! Intra-arterial chemotherapy did have less systemic side effects comparing to intravenous chemotherapy in our study and many publications.

CONCERNS:

Comment 4: the paper needs to be reviewed and re-written by a native English speaker or an appropriate service. Some of the sentence structures and phrasing was very awkward and made it difficulty to read the paper

Reply 4: I'm really apologize for some sentence structure and phrasing of the original manuscript have brought obstacles to smooth reading, and the revised manuscript has been reviewed and revised properly by MedSci.

Comment 5: I am unclear on if patients were pre-treated with antiemetics for their

intravenous chemotherapy, as this would be standard of care. It would also be important for the reader to know which chemotherapy agents were given and what their emetogeneticy classification is (see Dupuis et al 2013, https://www.ncbi.nlm.nih.gov/pubmed/23512831) and also adjust for these medications in the multivariate analysis. If the guidelines weren't followed it would be important to discuss why not.

Reply 5: Thank you for your comments! All our patients were pre-treated with antiemetics for their intravenous chemotherapy. We agree with you that the reader should know which chemotherapy agents were given and what their emetogenicity classification are very important. The use of chemotherapy agents in our RB children was in line with the guidelines, which were presented as intraarterial/intravenous chemotherapy and detailed medications were also provided. These medications have been adjusted in multivariate analysis, but in the name of administration mode.

Changes in the text:

1. We use VEC regimen(vincristine, etoposide, and carboplatin) in IVC group , and melphalan, topotecan ,carboplatin in IAC group. The mean duration of chemotherapy block was 1-2 days. Among the drugs used in chemotherapy for RB patients, carboplatin has a moderate risk of vomiting (0~90%), etoposide and topotecan have a low risk of vomiting (10~30%), and vincristine and melphalan have a slight risk of vomiting (< 10%)(20). All children used a two-drug combination of ondansetron and dexamethasone to prevent vomiting caused by chemotherapy after general anesthesia. (see Page 5, line 106-112)
2. In the absence of preventive drugs, moderately emetogenic chemotherapy (MEC) could cause CINV in 30-90% of cases, while the incidence of CINV with the low emetogenic chemotherapy was reported in the range of 10-30% (9). Patients-associated factors have significantly influenced the risk of CINV, such as history of nausea/vomiting, female gender, younger age, and history of morning sickness(10). (see Page 3, line 106-112)
3. Analyses were adjusted for age, gender, laterality at diagnosis, presence of ocular enucleation, and auxiliary medicine. (see Page 8, line 180-181)

Comment 6: I'm assuming that the patient receiving IAC and IVC received multiple cycles of chemotherapy. Was just the first cycle analyzed or are there multiple cycles included per patient.

Reply 6: This is a limitation of our study, that is, the data includes multiple cycles of patients. Although the impact of these two situations on the results is always statistically significant as to whether the statistical variance comes from within or between individuals. In the field of Ophthalmology, researchers usually identify the repeated measurement data or comparative data as multiple individuals in a pilot study, in order to find some clinical trends. Statistically rigorous research will be performed in further study.

Changes in the text: Among the 803 cases reviewed in this study, the majority of them were children who were repeatedly hospitalized. Whether CIV differs among RB children with different hospitalization periods should be further studied. (see Page11,

line 266-268)

Comment 7: acute chemotherapy induced vomiting is defined as any vomiting within 24 hours of last chemotherapy dosing. What is the time period during which vomiting was measured? and when was the vomiting in relation to anesthesia. Did all the patients receive anesthesia, even if they received only IVC?

Reply 7: In the original manuscript, our statement on vomiting caused by acute chemotherapy is puzzling and has been corrected. Vomiting was measured within 24 hours of last chemotherapy dosing. All patients included in this study received general anesthesia, so the vomiting we investigated was caused by the dual action of anesthesia and chemotherapy drugs. The main index of the study has been modified to vomiting caused by chemotherapy after general anesthesia.

Changes in the text:

1. The scope of this study was limited to the emergence of vomiting in the acute phase (i.e., 24-h period following administration of chemotherapy) and did not include anticipatory, breakthrough or delayed phase, or radiation-related vomiting. (see Page 6, line 134-137)
2. The inclusion criteria were as follows: all children with RB who aged <5 years old, underwent fundus examination under general anesthesia, and only received chemotherapy block. After waking up in the recovery room for 2 h, patients returned to the ward and underwent chemotherapy. (see Page 5, line 121-124)
3.The primary study endpoint was the times of vomiting in children with RB under the dual effects of chemotherapy and general anesthesia. (see Page 6, line 126-127)

Minor comments:

Comment 8: difference in platelet counts between vomiting versus non vomiting group is not clinically significant (although apparently statistically significant). I wouldn't include this variable

Reply 8: We agree with you very much. Although there are obvious statistical differences in platelet values between groups, the clinical difference is not significant. Expanding the prior knowledge of treatment and nursing related to this disease is also one of the purposes of our research team. This variable is included in this model in order to try to make a further detailed discussion on platelet changes in the following study, such as grading platelets according to other physiological indexes of patients, but this study alone cannot fully achieve it at present.

Comment 9: I wouldn't include the anesthesia medications

Reply 9: Vomiting in this study actually occurred under the double effects of anesthetics and chemotherapeutic medications. For a more accurate description, we have revised the title of the article.

Changes in the text: Risk factors for chemotherapy-induced vomiting after general anesthesia in children with retinoblastoma: A retrospective study (see Page1, line1)

Comment 10: should be ocular enucleation not "eyeball"

Reply 10: Thank you for your comments! In the revised manuscript, all "eyeball" has been replaced by "ocular enucleation ".
Changes in the text: (see Page 3, line 54), (see Page6, line 130), (see Page7, line 162), (see Page8, line 177)

Comment 11: would not include the section on alternative medications for the use of CINV unless that was specifically studied in these patients
Reply 11: We also conducted a special study on the management of these patients after vomiting, and supplemented the relevant contents in the revised manuscript after detailed elaboration.
Changes in the text:
1. Table 2 The effects of auxiliary antiemetics

Group	Total	Slightly relieved	Complete relieved	X^2 value	*P*-value
Ondansetron	47	11(23.4%)	36(76.6%)		
Metoclopramide	96	45(46.9%)	51(53.1%)	7.31	0.026
No-antiemetics	12	5(41.7%)	7(58.3%)		

CIV= chemotherapy-induced vomiting; RB = Retinoblastoma.
2. The effects of auxiliary antiemetics
The results of Chi-square test showed that different interventions have different relief effects on vomiting (P = 0.026). Pair-wise comparison demonstrated that ondansetron has a superior overall relief compared with metoclopramide (P=0.007), indicating no significant difference among the observation, ondansetron, and metoclopramide groups (Table 2). (see Page 7, line168-172)
3. There was a statistically significant difference in the incidence of vomiting among children who did not take medicine, ondansetron or metoclopramide, and ondansetron was superior to metoclopramide. Although it is an indisputable fact that the central antiemetics are more reliable than the peripheral antiemetics, this conclusion was at least verified for the first time in the subgroup of RB children receiving arterial/venous chemotherapy. Additionally, the results showed no significant difference in vomiting among the observation, ondansetron, and metoclopramide groups, which might be related to the small sample size (n=12) of the observation group. (see Page 8-9, line197-205)

Reviewer B
Comment 1: This manuscript aims to identify risk factors for vomiting in patients with retinoblastoma who are less than 5 yrs old. It could be improved by 1) drawing on current literature and guidance regarding chemotherapy-induced vomiting (CIV) and post-operative vomiting (POV) and 2) applying methods more in line with CIV study methods and 3) recognizing the limitations of their dataset.
Reply 1: Thank you for your advice! Firstly, in the **Introduction** section, we review and supplement the current literature and guidelines on chemotherapy-induced vomiting (CIV) and postoperative vomiting (POV). Secondly, this study is a retrospective study. It is not intended to recruit research subjects to study the vomiting

caused by chemotherapy after general anesthesia in children with RB, which may lead to some influencing factors out of control. However, the results of this study can provide reference for the follow-up prospective research. Finally, the dataset includes multiple cycles of patients. This is a limitation of our study. Although the impact of these two situations on the results is always statistically significant as to whether the statistical variance comes from within or between individuals. In the field of Ophthalmology, researchers usually identify the repeated measurement data or comparative data as multiple individuals in a pilot study, in order to find some clinical trends. Statistically rigorous research will be performed in further study.

Changes in the text:

1. In the absence of preventive drugs, moderately emetogenic chemotherapy (MEC) could cause CINV in 30-90% of cases, while the incidence of CINV with the low emetogenic chemotherapy was reported in the range of 10-30% (9). Patients-associated factors have significantly influenced the risk of CINV, such as history of nausea/vomiting, female gender, younger age, and history of morning sickness (10). (see Page3, line 71-75)
2. The 2021 clinical practice guideline is strongly recommended to optimize acute and delayed CINV control to prevent anticipatory CINV(12). (see Page4, line 77-78)
3. PONV is a frequent complication in pediatric patients undergoing general anesthesia. To date, several studies have identified PONV-associated risk factors. Rüsch et al. (14) found that female gender, history of PONV, motion sickness, intraoperative and postoperative administration of opioids, use of inhaled anesthetics and nitrous oxide, and anesthesia time were the relevant risk factors of PONV. Dupuis et al. (15) demonstrated that younger age, administration of antiemetic prophylaxis, shorter acute-phase duration, and antiemetic regimen were associated with complete control of chemotherapy-induced vomiting (CIV) in pediatric patients receiving MEC or HEC. Gan et al. (16)described specific risk factors for postoperative vomiting (POV) in children (age >3 years old, eye surgeries, duration of surgery >30 min, family history, etc.). An exploratory study (17) found that the number of platelets was associated with the occurrence of PONV. The platelet count, mean platelet volume and their ratio may be used to predict POV in children (18). Karaca et al. (19)reported that platelet-to-lymphocyte ratio (PLR) or neutrophil-to-lymphocyte ratio (NLR) could be used to predict inflammatory diseases. They pointed out that preoperative NLR and PLR could be considered in antiemetic regimens to prevent PONV. (see Page4, line 84-98)
4. Among the 803 cases reviewed in this study, the majority of them were children who were repeatedly hospitalized. Whether CIV differs among RB children with different hospitalization periods should be further studied. Hence, some prospective studies can be designed in the future to recruit patients purposefully, and to verify whether the differences among chemotherapy regimens and results of clinical tests obtained from this study are the decisive factors that can affect CIV, indicating the necessity of developing further predictive interventions. (see Page11, line266-272)

Comment 2: Title: I think the word ‘observational’ can be deleted.

Reply 2: Thank you for your advice! We deleted the word "observation" in the title of

the revised manuscript.
Changes in the text: Risk factors for chemotherapy-induced vomiting after general anesthesia in children with retinoblastoma: A retrospective study (see Page 1, line 1)

Comment 3: Introduction: The unique aspect of this study is the patient population selected, the administration of intra-arterial chemotherapy and that patients, at least during some chemotherapy blocks, may experience both CIV and POV. I expected to read more about these entities in children and to have the current CIV and POV clinical practice guidelines discussed. It would be helpful to end the Introduction to explicitly state the hypothesis that drives this study. Do you believe that children with RB are at higher risk of vomiting than patients with other cancers because they receive chemotherapy and surgery concurrently?
Reply 3: Thank you very much for your comments! All children with RB included in this study underwent fundus examination under general anesthesia and then chemotherapy. Compared with other children suffered from cancer, they have a higher risk of vomiting because they receive chemotherapy and surgery under general anaesthesia concurrently. In the **Introduction** section of the revised draft, we supplemented some of the current CIV and POV clinical practice guidelines.
Changes in the text:
1. In the absence of preventive drugs, moderately emetogenic chemotherapy (MEC) could cause CINV in 30-90% of cases, while the incidence of CINV with the low emetogenic chemotherapy was reported in the range of 10-30% (9). Patients-associated factors have significantly influenced the risk of CINV, such as history of nausea/vomiting, female gender, younger age, and history of morning sickness (10). (see Page3, line 71-75)
2. The 2021 clinical practice guideline is strongly recommended to optimize acute and delayed CINV control to prevent anticipatory CINV(12). (see Page4, line 77-78)
PONV is a frequent complication in pediatric patients undergoing general anesthesia. To date, several studies have identified PONV-associated risk factors. Rüsch et al. (14) found that female gender, history of PONV, motion sickness, intraoperative and postoperative administration of opioids, use of inhaled anesthetics and nitrous oxide, and anesthesia time were the relevant risk factors of PONV. Dupuis et al. (15) that younger age, administration of antiemetic prophylaxis, shorter acute-phase duration, and antiemetic regimen were associated with complete control of chemotherapy-induced vomiting (CIV) in pediatric patients receiving MEC or HEC. Gan et al. (16)described specific risk factors for postoperative vomiting (POV) in children (age >3 years old, eye surgeries, duration of surgery >30 min, family history, etc.). An exploratory study (17) found that the number of platelets was associated with the occurrence of PONV. The platelet count, mean platelet volume and their ratio may be used to predict POV in children (18). Karaca et al. (19) reported that platelet-to-lymphocyte ratio (PLR) or neutrophil-to-lymphocyte ratio (NLR) could be used to predict inflammatory diseases. They pointed out that preoperative NLR and PLR could be considered in antiemetic regimens to prevent PONV. (see Page4, line 84-98)

Comment 4: Page 3, line 69: While I can accept that clinicians in general do not pay sufficient attention to CINV assessment and management, you seem to be making the point that clinicians who care for patients with retinoblastoma are particularly bad at this. Please explain why this is the case.

Reply 4: We are sorry for the puzzling expression. What we really mean is that clinicians who treat retinoblastoma patients are more concerned about the therapeutic effect of chemotherapy on ocular tumors of RB children than CINV.

Changes in the text: In this specific population, ophthalmologists have paid more attention to the therapeutic effects of chemotherapy on ocular tumors, while gastrointestinal complications, such as chemotherapy-induced nausea and vomiting (CINV) or postoperative nausea and vomiting (PONV) have been scarcely studied. Owing to the necessity of assessment and management of CINV or PONV, they currently do not belong to the routine diagnostic and therapeutic schemes in ophthalmology. (see Page 3, line 60-65)

Comment 5: Page 3, line 76-89: This paragraph is very confusing. It is not possible to appreciate CIV rates without understanding the emetogenicity of chemotherapy received, the antiemetic prophylaxis received and the phase of chemotherapy being assessed. The sentences where reference 10 and 11 are cited merely state the standard definitions for HEC and MEC.

Reply 5: Thank you for your comments. We have amended and supplemented this paragraph. References 10 and 11 in the original manuscript have been deleted.

Changes in the text:

1. In the absence of preventive drugs, moderately emetogenic chemotherapy (MEC) could cause CINV in 30-90% of cases, while the incidence of CINV with the low emetogenic chemotherapy was reported in the range of 10-30% (9). Patients-associated factors have significantly influenced the risk of CINV, such as history of nausea/vomiting, female gender, younger age, and history of morning sickness(10). (see Page 3, line 71-75)
2. The 2021 clinical practice guideline is strongly recommended to optimize acute and delayed CINV control to prevent anticipatory CINV(12).(see Page 4, line 77-78)

Comment 6: Page 3, line 91-96: Recent studies identifying CIV and POV risk factors in pediatric patients have been omitted. For example, Dupuis et al JCO 2020 found that age, antiemetic prophylaxis received and chemotherapy block duration are predictors of acute phase CIV in children receiving MEC or HEC and acute phase COV predicts delayed phase CIV. The clinical practice guideline cited later (#26) identified acute phase CINV as a predictor of anticipatory CINV. Similarly, Gan et al Anaesth Anal 2020 describe specific risk factors for POV in children (age > 3 yrs, family history, type and duration of surgery, etc). Interestingly, platelet count is not listed as a risk factor for POV. You might consider summarizing the literature supporting it as worthy of evaluation. This paragraph should be focused on pediatric literature and should serve to frame your choice of elements analyzed in your study.

Reply 6: Thank you for your advice! We supplement the recent research on identifying

CIV and POV risk factors in pediatric patients, including the results of the two scholars you recommended. The literature on platelet count as a risk factor for POV is also supplemented. The literature on platelet count as a risk factor for POV is also supplemented.

Changes in the text:

1. In the absence of preventive drugs, moderately emetogenic chemotherapy (MEC) could cause CINV in 30-90% of cases, while the incidence of CINV with the low emetogenic chemotherapy was reported in the range of 10-30% (9). Patients-associated factors have significantly influenced the risk of CINV, such as history of nausea/vomiting, female gender, younger age, and history of morning sickness (10). (see Page 3, line 71-75)
2. PONV is a frequent complication in pediatric patients undergoing general anesthesia. To date, several studies have identified PONV-associated risk factors. Rüsch et al. (14) found that female gender, history of PONV, motion sickness, intraoperative and postoperative administration of opioids, use of inhaled anesthetics and nitrous oxide, and anesthesia time were the relevant risk factors of PONV. Dupuis et al. (15) demonstrated that younger age, administration of antiemetic prophylaxis, shorter acute-phase duration, and antiemetic regimen were associated with complete control of chemotherapy-induced vomiting (CIV) in pediatric patients receiving MEC or HEC. Gan et al. (16)described specific risk factors for postoperative vomiting (POV) in children (age >3 years old, eye surgeries, duration of surgery >30 min, family history, etc.). An exploratory study (17) found that the number of platelets was associated with the occurrence of PONV. The platelet count, mean platelet volume and their ratio may be used to predict POV in children (18). Karaca et al. (19) reported that platelet-to-lymphocyte ratio (PLR) or neutrophil-to-lymphocyte ratio (NLR) could be used to predict inflammatory diseases. They pointed out that preoperative NLR and PLR could be considered in antiemetic regimens to prevent PONV. (see Page 4, line 84-98)

Comment 7: Page 4, line 10: This statement is untrue. See above comment.
Reply 7: Thank you for your advice! Incorrect statements have also been revised.

Comment 8: Page 4, line 105: The sentences about nausea and the median age of RB presentation seem out of place and should be deleted or moved to the methods or discussion.
Reply 8: Thank you for your advice! These two sentences have been deleted.

Methods:

Study Design:

Comment 9: Did patients contribute only a single chemotherapy block to the database?
Reply 9: Thank you for your question! Yes, the patients we studied only received chemotherapy blocking. In the revised manuscript, we made a more detailed supplementary explanation, that is, only chemotherapy blocking was used.
Changes in the text: The inclusion criteria were as follows: all children with RB who aged <5 years old, underwent fundus examination under general anesthesia, and only

received chemotherapy block. (see Page 5, line 121-123)

Comment 10: What was the permissible time period between receipt of general anesthesia and chemotherapy?
Reply 10: The permissible time period between receipt of general anesthesia and chemotherapy is about 2 hours.
Changes in the text: After waking up in the recovery room for 2 h, patients returned to the ward and underwent chemotherapy. (see Page 5, line 123-124)

Comment 11: Page 4, line 123-4: Please make sure that each data element abstracted from the chart appears in the analysis plan or delete it.
Reply 11: We supplemented relevant variables.
Changes in the text: The primary study endpoint was the times of vomiting in children with RB under the dual effects of chemotherapy and general anesthesia. We reviewed a large number of previous studies on predictive variables related to vomiting, combined with clinical experience and onset age of RB. Finally, the predictive variables of vomiting included in this study were age, gender, height, weight, laterality at the time of diagnosis, ocular enucleation, chemotherapy regimen, vomiting, auxiliary medicine, dexamethasone, anesthetics (e.g., midazolam, rocuronium, ketamine, sevoflurane), fundal examination time, duration of anesthesia, platelet count, and platelet distribution width.(see Page 6, line126-133)

Comment 12: Page 4, line125: The acute phase definition is not consistent with the definition traditionally used in CIV studies. Please revisit it and include the time of the fundal exam in it.
Reply 12: We revised the definition of the acute phase definition in the **Study design** section of the revised manuscript.
Changes in the text: The scope of this study was limited to the emergence of vomiting in the acute phase (i.e., 24-h period following administration of chemotherapy) and did not include anticipatory, breakthrough or delayed phase, or radiation-related vomiting. In the present study, vomiting was defined as retching and expulsion of the stomach's contents through the mouth. Vomiting events with an interval of more than 1 min were regarded as two independent vomiting events. (see Page 6, line 134-139)

Comment 13: Page 4, line 129: Shivering and salivation are not included in the usual definition of vomiting. Please justify.
Reply 13: We agree with that shivering and salivation are not included in the definition of vomiting. We have deleted them in the revised draft.

Comment 14: Page 4, line 130: It seems odd to say that you 'designed' a nursing record sheet when describing a retrospective study. Do you mean to say that it was a practice standard for nurses to record the listed information on a standardized form?
Reply 14: Sorry, we didn't express this sentence clearly. As you understand, what we want to express is that in daily nursing practice, our nursing team has recorded the

relevant information about vomiting on a standardized form. We have changed this sentence to 'It was a practice standard for nurses to record the listed information on a standardized form, which was stored in the medical record.' in the revised manuscript.
Changes in the text: It was a practice standard for nurses to record the listed information on a standardized form, which was stored in the medical record. (see Page 6, line 140-142)

Comment 15: Page 4, line 132: The usual definition of a vomiting episode is that there be at least 1 minute between episodes. Why was the color, quantity (volume?) and shape of the vomit collected? How did it inform your analysis?
Reply 15: The definition of a vomiting episode is that there is at least 1 minute between episodes, and we have revised them in the revised manuscript.The color, volume and shape of vomit are listed in our standard form, but they are not the variables we focus in this study. We have deleted the relevant contents in the revised manuscript. (see Page 6, line 138-142)

Comment 16: Page 4, line 133: I do not understand the reference to 'controls' since this is not a comparative study and controls have not yet been mentioned in the Methods.
Reply 16: Thank you for your comments. The statement of the 'controls' may indeed be inappropriate. We just want to express the baseline of patients. We delete this expression in the revised manuscript.

Comment 17: Statistical analysis:
Please state what your primary study endpoint is.
Reply 17: The primary study endpoint of our study was the times of vomiting in children with RB under the dual effects of chemotherapy and anesthesia. We have made supplementary explanations in the statistical part of the revised manuscript.
Changes in the text: The primary study endpoint was the times of vomiting in children with RB under the dual effects of chemotherapy and general anesthesia. (see Page 6, line 126-127)

Comment 18: Given the stated study aim, I don't understand why independent sample comparisons were performed. Please explain the limitations on the number of possible predictive factors that could be evaluated and the choice of possible predictive factors for analysis and list them. Please explicitly state that a multivariable analysis was taken.
Reply 18: 1. We performed independent sample comparisons to make a preliminary judgment at the beginning of the study to find out whether there are some factors that have a great impact on the results. If such variables exist and are clinically interpretable, we will tend to conduct stratified studies on cases. In this study, we did not find such variables, so the following analysis was not stratified and multivariable analysis was directly done.
2. The research team consulted a large number of literature on vomiting related predictors, but considering the specificity of children with RB, such as the young age of onset, the vomiting predictors included in this study are limited due to the availability

in clinical practice.
3. In the part of statistical analysis, we now state that multivariate analysis was taken.
Changes in the text:
1. We reviewed a large number of previous studies on predictive variables related to vomiting, combined with clinical experience and onset age of RB. Finally, the predictive variables of vomiting included in this study were age, gender, height, weight, laterality at the time of diagnosis, ocular enucleation, chemotherapy regimen, vomiting, auxiliary medicine, dexamethasone, anesthetics (e.g., midazolam, rocuronium, ketamine, sevoflurane), fundal examination time, duration of anesthesia, platelet count, and platelet distribution width.(see Page 6, line 127-133)
2. Univariate analysis was conducted first, then multivariate logistic regression analysis was undertaken for finding significant variables ($P<0.05$) and borderline significant variables. (see Page 6-7, line 150-152)

Results
Comment 19: Patient characteristics: You stated that you evaluated 803 children who diagnosed over a 3-yr period. This is about 25% of all children diagnosed with RB in all of China during that period. Please confirm and explain the size of your institution in the Methods. Please do not repeat data that are presented in the Tables.
Reply 19: Thank you for your comments. We reviewed 803 hospitalized medical records of children with RB. Most children received repeatedly hospitalization for chemotherapy. Each admission of children is recorded as a chemotherapy event in this study. This is also one of the limitations of this study, which is listed in the limitations section. In the result part of the revised manuscript, the data in the table is not simply repeated, but summarized.
Changes in the text:
1. Among the 803 cases reviewed in this study, the majority of them were children who were repeatedly hospitalized. Whether CIV differs among RB children with different hospitalization periods should be further studied. Hence, some prospective studies can be designed in the future to recruit patients purposefully, and to verify whether the differences among chemotherapy regimens and results of clinical tests obtained from this study are the decisive factors that can affect CIV, indicating the necessity of developing further predictive interventions. (see Page 11, line 266-172)
2. The mean values of age, weight, height, and platelet count of the children in this survey were 2.35 years old, 13.44 kg, 88.70 cm, and $276.31 * 10^9$/L, respectively. The male :female ratio was within 1:1. Of the 803 patients, RB patients were mainly unilateral (77.8%), and ocular enucleation rate was low (7%). VEC regimen was dominantly used in our center, and arterial IAC regimen account for only 33.2%. Although we followed the guidelines and all children received a combination of 5-HT3 receptor antagonist and dexamethasone to prevent vomiting, the incidence of CIV was 19.3% (155/803), and auxiliary medicine was administered to 92.3% (143/155) of patients who suffered from vomiting (Table 1).(see Page 7, line 160-167)

Comment 20: It appears that most patients did not receive clinical practice guideline-

consistent CIV prophylaxis.

Reply 20: Sorry, we didn't make it clear that all patients included in this study received CIV prophylaxis consistent with clinical practice guidelines. Dexamethasone was used in all children during anesthesia, and ondansetron was used to prevent CIV before chemotherapy.

Changes in the text: Although we followed the guidelines and all children received a combination of 5-HT3 receptor antagonist and dexamethasone to prevent vomiting, the incidence of CIV was 19.3% (155/803), and auxiliary medicine was administered to 92.3% (143/155) of patients who suffered from vomiting (Table 1).(see Page 7, line 164-167)

Comment 21: Table 1: What chemotherapy agents were given and what was their emetogenicity classification as per the clinical practice guideline by Paw Cho Sing PBC 2020? What was the mean chemotherapy block duration? How was surgery or evaluation under anesthesia timed with respect to chemotherapy administration? What anesthetic agents were given? What was the mean duration of anesthetic exposure? What opioids did patients receive post-op during the acute phase?

Reply 21: Sorry, many details were not stated clearly enough. In the preface, we pointed out the drugs used in chemotherapy for RB patients and listed their emetic classification according to the clinical practice guidelines of paw Cho sing PBC 2020. The average duration of chemotherapy block was 2 days. Surgery or evaluation under anesthesia was performed first, and then chemotherapy was given. The anesthetics used include midazolam, ketamine, sevoflurane and rocuronium. The dose of these anesthetics and the average duration of anesthesia exposure are 58 minutes, which are supplemented in Table 1. Patients in the acute phase did not use opioids after operation.

Changes in the text:

1. We use VEC regimen(vincristine, etoposide, and carboplatin) in IVC group , and melphalan, topotecan ,carboplatin in IAC group. The mean duration of chemotherapy block was 1-2 days. Among the drugs used in chemotherapy for RB patients, carboplatin has a moderate risk of vomiting (0~90%), etoposide and topotecan have a low risk of vomiting (10~30%), and vincristine and melphalan have a slight risk of vomiting (< 10%)(20). All children used a two-drug combination of ondansetron and dexamethasone to prevent vomiting caused by chemotherapy after general anesthesia. (see Page 5, line 106-112)
2. The inclusion criteria were as follows: all children with RB who aged <5 years old, underwent fundus examination under general anesthesia, and only received chemotherapy block. After waking up in the recovery room for 2 h, patients returned to the ward and underwent chemotherapy. (see Page 5, line 121-124)

Comment 22: Were antiemetics given on a scheduled basis to prevent vomiting or to treat vomiting when it occurred? What proportion of patients received both ondansetron and metoclopramide? What does ‘observation’ mean – no antiemetics given? Dexamethasone is listed in Table 2. Why is it not listed here as an antiemetic?

Reply 22: Antiemetics given to treat vomiting when it occurred. No patients were

treated with both ondansetron and metoclopramide. ‘observation’ means – no antiemetics given, and we have revised it in the revised version. Dexamethasone is only used during anesthesia. The antiemetic drugs listed in Table 1 are the drugs used when the patient vomits after chemotherapy, excluding dexamethasone.

Comment 23: Table 2: With 155 patients who vomited, 15 factors can be assessed. Nineteen factors were analyzed. Please reconsider/justify. What is an ‘Auxiliary medicine’?
Reply 23: For 155 patients with vomiting, 19 factors were be evaluated. The expression of " Auxiliary medicine " is not accurate enough, so we modify it to " Manage of CIV ".

Comment 24: Table 3: Please explain the meaning of ‘’B’.
Reply 24: B refers to the regression estimate, which we have footnote and table 4 below.