Reviewer #1:

The manuscript by Xu et al. entitled "Relationship between plasma risperidone concentrations and clinical features in chronic schizophrenic patients in China" presents an interesting report showing that risperidone and 9-hydroxy risperidone have a significant effect in women and older patients and recommends considering this finding to adjust doses in patients to achieve a more substantial benefit from the therapeutic capabilities of risperidone. The manuscript is very well elaborated and presented; I only recommend abounding on the systemic effects that induce the consumption of this antipsychotic, for which I recommend the following review doi: 10.3389/fend.2020.00195

Reply: Thank you for your positive feedback on our study, and we appreciate your valuable comments. The review you recommend has been added as a reference.

Reviewer #2:

ABSTRACT “The present study assessed physical situation, psychopathology and functionality of the patients and explored the associations and correlations between clinical variables and plasma levels.”

1.It is not clear what the term “physical situation” means.

Reply: Thank you for reminding me. It has been modified in the article.

2. In the Methods section of the main manuscript (Study Variables and Questionnaire), there is no mention of a scale to measure functioning (functionality)

Reply: I appreciate the reviewer's attention to detail. 'Functionality' has been removed.

3. On the other hand, severity of depression was rated on the PHQ-9. This is not mentioned here. “Significantly the men received higher doses of risperidone than the women, risperidon+9-hydroxyrisperidone （active moiety)/dose 、risperidon+9-hydroxyrisperidone / (dose × kg) were higher in the women.”

Reply: Thank you for raising this point.The PHQ-9 was used to screen for depression in instances of possible serious depression ,but we did not find individuals with severe depression .

4. Doses and plasma concentrations in men and women should be included.

Reply: Thank you for your advice. “Doses and plasma concentrations in men and women” are showed in table2.

INTRODUCTION 5. The authors fail to mention a significant fact about the receptor binding profile of risperidone, which might have influenced their results. Risperidone has a high 5-HT2A/D2 ratio, which should protect against extrapyramidal symptoms. However, at higher doses, risperidone produces significant EPS, indicating that 5-HT2A antagonism alone cannot eliminate EPS associated with substantial D2 receptor blockade (Marder SR, Meibach RC. Risperidone in the treatment of

schizophrenia. The American Journal of Psychiatry. 1994;151(6):825-35).
Reply: Thank you for your feedback and concerns. Based on your feedback, we have added this into the discussion.

6. Although therapeutic drug monitoring is recommended for all psychotropics, one wonders if it is practical to measure plasma risperidone and its metabolites in routine clinical practice.
Reply: Thank you for your suggestion. In response to your feedback, the sentence can be revised as follows:"We recommend，if the conditions permit，measuring plasma risperidone and its metabolites in routine clinical practice .We have added this into the discussion."

METHOD
7. The PHQ-9 might not be an appropriate instrument to rate the severity of depression in schizophrenia.
Reply: We appreciate your inquiry about the profiles of depression and PHQ-9. We use PHQ-9 for primary screening of depression, and if one get a score ＞ 15, further measure will be performed. But we did not find individuals with severe depression .

8. It is not clear why concentrations risperidone+9-hydroxyrisperidone in plasma had to be estimated.
Reply: Thank you for raising this point.The sum of the plasma concentrations of risperidone and 9-hydroxyrisperidone is referred to as the clinically relevant "active moiety".

9. Taking trihexyphenidyl is not a suitable proxy measure for the presence of EPS because it is often prescribed indiscriminately. The authors should have used a standard scale or at least an unstructured rating of EPS on examination.
Reply: Thank you for your advice.This is a cross-sectional survey. Because the vast majority of participants who have been administering anticholinergic therapy for some time, EPS has been significantly alleviated and cannot be detected by an interview. So we chose the use of anticholinergic drugs as criteria for EPS.

10. Similarly, it is not clear why the authors chose to examine only EPS and constipation as side effects, when other side effects such as sedation, weight gain, and others are far more common.
Reply: Thank you for your advice. The intended meaning is that all patients have been treating with risperidone for a long time. So this cross-sectional study could not detect whether sedation or weight gain had occurred recently.

RESULTS
11. Some of the findings are not new or unusual. Men received higher doses but this

could be a function of the predominance of men in a relatively small sample.
Reply: I appreciate the reviewer's attention to detail. You are correct， we have added this into the discussion.

12. Women had significantly higher levels of risperidone and risperidon+9-hydroxyrisperidone, whereas men had non-significantly higher levels of 9-hydroxyrisperidone. I think apart from age, the sex difference is the only notable finding of this study. However, the other gender difference, that is a significant association between risperidone+9-hydroxyrisperidone levels and PANSS scores only in men has not been highlighted properly.
Reply: Thank you for your valuable feedback. In response to your feedback, we have added this into the discussion.

13. Similarly, the lack of association between EPS and risperidone levels has not been explained adequately.
Reply: Thank you for pointing out the discrepancy. In response to your feedback, the sentence can be revised as follows:“A further limitation of this study is the lack of an association between EPS and risperidone levels”

DISCUSSSION “The characteristics of the sample are those which could be expected based on previous studies of groups of patients with resistant schizophrenia..”
14. This comes as a surprise because there is no mention of patients meeting criteria for treatment-resistant schizophrenia.
Reply: Thank you for pointing out the error. It's chronic schizophrenia. It has been modified in the article.

15. The authors must realize that their sample size is small and methodology not quite perfect. Therefore, conclusions such as “risperidone at therapeutically effective plasma concentration does not seem to predispose patients to QTc interval lengthening” may be quite misleading.
Reply: Thank you for your valuable feedback. We have added this into the discussion as follows: “Regarding the small sample size， this result has to be interpreted carefully.”

16. This study has serious methodological limitations, but these have hardly been mentioned.
Reply: We appreciate the reviewer's insightful comments regarding the methodological limitations in our article. Since this study was a cross-sectional survey, mainly chronic patients, a small sample size, and the research data were mainly derived from laboratory analysis and medical records （for example， taking trihexyphenidyl \laxatives or not）, so that's why this study has serious methodological limitations. We hoped that further research can reach more convincing conclusions.

LANGUAGE

17. The text needs to be edited by a professional.

Reply: Thank you for your advice. We have sent the text to a professional editor to recheck and refine the language of this article.